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VOL. II.—31ST YEAR. SYDNEY, SATURDAY, NOVEMBER 4, 1944. No. 19.

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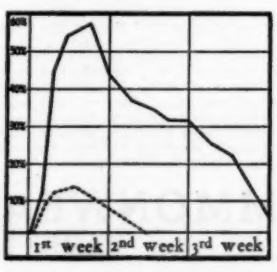

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PENICILLIN: AN INVESTIGATION AND CLINICAL TRIAL.

By R. OFFICER, F.R.C.S., F.R.A.C.S.,
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THE discovery and clinical use of penicillin have opened a new and brilliant page in the history of both surgery and medicine. The purpose of this paper is to record a clinical and laboratory study of 141 cases in which treatment with penicillin was used, and to discuss the methods employed and the results, in the light of recent researches in England and America.

In March, 1944, the Director-General of Medical Services arranged for this work to be undertaken in an Australian military hospital in collaboration with the Director of the Commonwealth Serum Laboratories and a specially trained staff led by Major P. L. Bazeley.

The preparations of penicillin used throughout these investigations were manufactured in Australia. Three salts of Penicillin "Commonwealth" were supplied, namely sodium, "crude" calcium and "refined" calcium.

To use penicillin effectively in the treatment of patients, its limitations must be recognized. To overcome these limitations thorough knowledge of its properties and close cooperation between bacteriologist and medical practitioner are necessary. It must be realized that penicillin is active against a limited number of organisms and the preparations at present available are unstable, especially when in solution.

Penicillin belongs to a class of antibacterial agents termed "antibiotics", in contradistinction to "antiseptics". Antibiotics are the product of the growth of bacteria or of moulds, which prevent the proliferation of other organisms.

DISCOVERY OF PENICILLIN.

Antibiotics have been known since the time of Pasteur, but the earliest antibiotic studied was pyocyanase, a product of *Bacillus pyocyaneus*, discovered at the end of the last century. Most of the antibiotics, although active against bacteria, have proved toxic when administered to animals or human beings; but penicillin, as well as being strongly active against bacteria, is almost completely free of toxic reactions in human beings.

Penicillin was discovered and named by Professor Fleming in 1929.[1] At that time, research that he was carrying out necessitated frequent examination of culture plates of *Staphylococcus aureus*. One of these plates was left on the laboratory bench and became contaminated with a mould. Fleming noticed, as this mould colony grew, that surrounding colonies of staphylococci disappeared. Subcultures of the mould, whose morphology was thought to be that of *Penicillium rubrum*, were made in nutrient broth and after they had grown for two weeks Fleming found that the broth had acquired the property of inhibiting the growth of many pathogenic bacteria. Fleming gave the name "penicillin" to the broth filtrate, but since that day the term has been applied to the active principle produced by the mould. He found that penicillin was unstable and particularly sensitive to heat, and to an acid or alkaline medium. He tried the effect of the drug on chronically infected ulcers with some success. Owing to the toxicity of the mixture of the penicillin and nutrient broth, clinical trial was not carried further. Since then Fleming has used penicillin as a differential culture medium for organisms insensitive to the drug. Recently, further penicillin-producing moulds have been found, but the greater part of therapeutic penicillin produced today is obtained from subcultures of Fleming's original mould.

In 1932 Clutterbuck, Lovell and Raistrick[2] published their investigations into the Fleming mould. They reclassified the mould as *Penicillium notatum* and cultured it on a synthetic medium which gave a higher yield of the active substance. Modifications of this medium are being used today in the production of penicillin for therapeutic use.

In 1938 Professor Florey[3] and his associates at Oxford decided to attempt the purification of penicillin in order to study its bacteriological and chemical properties. After a

lengthy study they were able to obtain it in a relatively pure state and it is a direct result of their work that penicillin is now available for clinical use.

THE GROWTH OF PENICILLIUM NOTATUM.

The mould is grown on a shallow layer of a synthetic culture medium which produces almost 200 times as much penicillin as the media used by Florey in his early work.

Spores of *Penicillium notatum* are sown into large flat glass bottles containing the medium in a depth of 1·5 to 2·0 centimetres.[4] The bottles are incubated at 24° to 26° C. The mould grows poorly at higher temperatures and at 37° C. no penicillin is produced. After two days a fluffy white growth appears in the fluid and reaches the surface on the third day. By the eighth day the surface growth has become a thick corrugated felt of a greenish-blue colour with droplets of yellow fluid on its surface. (Figure I.)

The culture medium is so prepared that its reaction is neutral. During the first few days of growth the reaction becomes acid, but as growth increases the substrate becomes neutral and then alkaline. The penicillin content is at its maximum when the hydrogen ion concentration is in the region of 7, that is, on the eighth to the tenth day. If growth is allowed to proceed, the pH rises to 8 to 9 and the greater part of the penicillin is destroyed. Therefore harvesting is carried out before the culture medium becomes too alkaline.[4] [5] When the mould is cultivated great care must be taken to avoid contamination with air-borne bacteria because many of these produce a substance capable of destroying penicillin.

PROPERTIES OF PENICILLIN.

Physical Properties.[1] [2] [4] [5] [6]

The active principle found in the culture medium is an unstable acid. It is easily soluble in organic solvents such as ether, chloroform, alcohol, amyl acetate and ethylene dichloride and in water. It readily forms salts with sodium, ammonium, calcium, barium and strontium ions.

Both acid and salts are unstable and are destroyed by heat and by acids and alkalis. Other destructive agents are heavy metals, primary alcohols, oxidizing agents and the products of some bacteria.

The following figures illustrate the effect of heat and hydrogen ion concentration on penicillin: (*a*) At a temperature of 30° C. and pH 4 no penicillin is detectable after 75 minutes in a solution originally containing 100 units per cubic centimetre. (*b*) At pH 10 and a temperature of 25° C. no penicillin is detected in a similar solution after two and a half days. (*c*) A solution of penicillin at pH 6–7, kept at or below 4° C., will retain its full activity for some weeks.

The Active Principle.

Penicillin is extracted from the crude broth by solution in amyl acetate at a temperature of 2° C. It is converted to the calcium salt, which is extracted from the amyl acetate by solution in water, its temperature still being maintained at 2° to 4° C. The calcium salt can then be further purified or converted during the stage of further purification to the sodium salt. The salts are unstable if kept in solution, consequently they are dried by subjection to a high degree of vacuum while in a frozen state. The sodium salt is the one supplied for general use, but as a result of our investigations it is considered that the "refined" calcium salt is as effective. Both are supplied in ampoules sealed *in vacuo*, and in this state, kept in the ice box (that is, 2° to 5° C.), they will retain their full activity for up to six months.

Unit of Activity.

As the chemical formula for penicillin has not yet been determined, there is no chemical test, either qualitative or quantitative, that can be applied to it; therefore the only means available for the testing of its potency is to measure its inhibitory action against bacteria.

Early in their work Florey[4] and his associates found that by adjusting a filtrate of crude broth to pH 6 to 7, saturating it with ether and keeping it at 0° C., it retained its potency for a period of months. They stated arbitrarily that this solution would represent one unit of potency per cubic centimetre, and found that this standard constantly gave a ring of inhibition 24 millimetres in diameter when tested by the Oxford cup method of assay. As a result of these findings they defined the unit of penicillin activity as "that amount of penicillin which, when dissolved in 1 cubic centimetre of water, gives a ring of inhibition the same as this standard". One unit of penicillin when dissolved in 50 cubic centimetres of nutrient broth will just inhibit the growth of the standard staphylococcus. This staphylococcus has been named "Staphylococcus H" (Heatley) and subcultures of it are used throughout the world for assaying the potency of penicillin products.

Different writers indicate in varying ways the strengths of the preparations used. Some give the weight of powder in milligrammes per cubic centimetre of fluid, while others express the amount as a dilution, for example, 1 in 100. Unless the strength in units of the original powder is known, comparison of activity is impossible. Throughout this paper the potency of all solutions and powders will be expressed as units per cubic centimetre, or units per gramme.

Effect of Blood, Pus and Tissue Extracts on Penicillin.

Blood, serum, pus and tissue autolysates have no destructive effect upon the potency of a solution of penicillin.[4] Serum and whole blood, in fact, enhance its activity.[7] In-vitro experiments show that organisms are more sensitive to penicillin in the presence of para-aminobenzoic acid and sulphapyridine.[8]

Toxicity.

Early preparations of penicillin, impure as they were (10 units per milligramme), were found when injected into animals to be toxic to a remarkably small degree.[3] No effects were found after instillation of crude broth into rabbits' eyes,[4] or after subcutaneous and intravenous injection in large doses. A 1:1,000 dilution of crude broth was absorbed into a rabbit's brain by osmosis.[4] No immediate disturbance was noted and autopsy six days later revealed no detectable change in the brain tissue. Preparations obtainable today are more refined (400 units per milligramme) and toxic effects are remarkable only by their absence. Experiments have been carried out to determine the effect of a relatively crude preparation on leucocytes and tissue cells.[4] [9] Leucocytes were killed by approximately 500 units per cubic centimetre, but were unaffected by 100 units per cubic centimetre. Fibroblasts were killed by 60 units per cubic centimetre, but survived in a concentration of eight units per cubic centimetre. All these are relatively high concentrations which are never attained in the human body when penicillin is administered by injection.

We are indebted to Dr. F. M. Burnet for investigations carried out on the toxic reaction of Penicillin "Commonwealth" on the chorio-allantoic membranes of chick embryos:

> Chorio-allantoic membranes of chick embryos were traumatized in order to produce fibroblastic reaction. Solutions of "crude" calcium, "refined" calcium, and sodium salts of penicillin in strengths of 500 units, 250 units, 100 units and 10 units per cubic centimetre were applied to the membranes twice daily for two days. Half of the eggs were examined at the end of two days and no diminution in fibroblastic reaction was detected and no reaction was seen in the surrounding membrane. The remainder were examined at four days and no diminution in fibroblastic reaction was found. The membranes subjected to the higher concentrations of penicillin of all three salts showed some haziness of the surrounding membrane, due to cellular infiltration.
>
> Two hundred and fifty units of sodium penicillin were injected intravenously into five twelve-day old chick embryos; all survived. As a result of these experiments it can be stated that the salts used were without toxic action on the delicate tissues of chick embryos.

Mode of Antibacterial Action.

It is difficult to determine whether penicillin acts as a bactericidal agent by direct action on the cells themselves or by interference with cell division. The weight of evidence which points strongly to the latter is summarized in the following observations *in vitro*:[10]

1. Penicillin acts either as a bacteriostatic or bactericidal agent depending on the conditions of the experiment, that is on the number and type of organisms present and the concentration of penicillin. A low concentration of penicillin will produce bacteriostasis, whereas higher concentrations have a killing effect.

2. Penicillin is effective only when multiplication is taking place. In the presence of a given concentration the rate of killing of organisms decreases as the culture progresses towards maturity. It has little appreciable effect in forty-eight hours on a fully grown culture when incubated at 37° C., whereas rapid sterilization of a fresh subculture is attained in a few hours. If multiplication of a young culture is impeded by low temperature, effect is reduced. At 0° C. penicillin effect and

growth are slight, but in the same culture incubated at 37° C. growth is rapid and killing effect maximal.

3. Within limits, the killing power of penicillin increases with rise in concentration, but beyond a certain point no greater effect occurs.

4. The rate of killing varies with different organisms and with different strains of the same organism.

5. No detectable amount of penicillin is destroyed or absorbed from solution by the organisms.

6. Lysis has not been found to accompany its action on staphylococci or hæmolytic streptococci.

7. Penicillin effect is gradual. In its presence in high concentration in a culture of staphylococci an inhibitory effect is first seen.[5] After two or more hours the number of living organisms present decreases progressively until 99% have been destroyed.[10] In lower concentrations the inhibitory effect continues.

8. Bacteria will grow in the presence of traces of penicillin, but in so doing they undergo morphological changes which suggest interference with reproduction.[11] Staphylococci show spherical enlargement of the cells and imperfect fission. Streptococci form longer chains and the individual cells are greatly swollen and some show pale granular staining (Figure II). Similar changes have been seen in cultures of *Clostridium welchii*. If these morphologically changed bacteria are subcultured in penicillin-free media, they return to their original state.

Penicillin does not cause the inhibition of growth of all bacteria. In Table I are listed those against which it is effective and those against which no effect is produced.

TABLE I.
Sensitivity of Various Organisms to Penicillin.

Sensitive.	Insensitive.
Gonococcus.	*Bacillus influenzæ.*
Pneumococcus.	*Bacillus coli.*
Meningococcus.	*Bacillus typhosus.*
Streptococcus pyogenes.	*Bacillus dysenteriæ.*
Streptococcus viridans.	*Bacillus proteus.*
Staphylococcus aureus.	*Bacillus paratyphosus* A.
Staphylococcus albus.	*Bacillus paratyphosus* B.
Clostridium welchii.	*Bacillus enteritidis.*
Vibrion septique.	*Bacillus pyocyaneus.*
Clostridium sporogenes.	*Bacillus prodigiosus.*
Clostridium œdematiens.	Friedländer's bacillus.
Clostridium sordellii.	*Bacillus tuberculosis.*
Clostridium histolyticum.	*Brucella abortus.*
Clostridium tetani.	*Brucella melitensis.*
Corynebacterium diphtheriæ.	*Vibrion choleræ.*
Treponema pallidum.	*Leptospira icterohæmorrhagiæ.*
Actinomyces.	*Monilia albicans.*
Bacillus anthracis.	Yeasts.
Bacillus subtilis.	

Different strains of a sensitive organism are found to vary in the degree of sensitivity and some strains, for example staphylococci, have been found to be relatively resistant.

Adaptation of Organisms to Penicillin.

Bacteria which are sensitive to penicillin have been found to become more resistant after growth for long periods in the presence of a concentration below that required to produce inhibition. This adaptation occurs in some strains only; it is not common to all. A strain of staphylococcus was grown for nine weeks in the presence of increasing amounts of penicillin and would finally grow in the presence of a concentration thirty times that which originally completely inhibited it.[4] No penicillin-destroying enzyme was found in the newly resistant organisms. Rammelkamp and Maxon[12] have rendered two strains of staphylococci 64-fold resistant in a period of seven weeks by in-vitro experiments. They found that staphylococci isolated from three out of fourteen patients showed marked increase in their resistance to penicillin after intervals varying from four to eighteen days. The sensitivity of staphylococci isolated from ten of our patients both before and after treatment is shown in Table II.

It will be seen that the organisms in three cases showed increased penicillin resistance, local therapy only being used in all. In one case in which local treatment was carried out for fifteen days, no effect was produced. In the six cases in our series in which penicillin was given by injection no increased resistance occurred. McKee and Houck[13] showed that an increase in resistance of staphylococci, streptococci and pneumococci obtained by in-vitro culture was accompanied by loss of virulence of the organisms to mice, and that repeated passage through mice failed to restore the virulence of the organisms.

TABLE II.
Development of Resistance of Staphylococci to Penicillin.

Strain Number.	Sensitivity Before Penicillin Treatment.	Days of Treatment.	Sensitivity After Penicillin Treatment.	Type of Treatment.
1	0·03	13	0·5	Local.
2	0·06	52	0·5	Local.
3	0·06	14	4·0	Local.
4	0·06	9	0·06	Intramuscular.
5	0·03	29	0·06	Intramuscular.
6	0·06	6	0·06	Intramuscular.
7	0·03	15	0·03	Local.
8	0·06	9	0·06	Intramuscular.
9	0·06	15	0·06	Intramuscular.
10	0·06	80	0·03	Intramuscular and local.

Destruction of Potency by Bacteria.

Abraham and Chain[14] found that an extract from crushed *Bacillus coli* contained a substance capable of destroying penicillin potency. They found that this substance resembled an enzyme which they named "penicillinase". Harper[15] has found penicillinase in culture filtrates and dried preparations of a paracolon bacillus, and in an air-borne micrococcus. The presence of penicillinase-producing organisms is of importance, first because the presence of such organisms in penicillin solutions rapidly destroys their potency, and secondly, penicillinase can be used to ensure growth in cultures made from penicillin-treated wounds. Half a milligramme of Harper's preparation was sufficient to counteract the effect of ten units of penicillin. If this paracolon bacillus preparation is incorporated in a culture medium and a smear from a penicillin-treated wound is applied, sensitive organisms will grow, whereas in the absence of penicillinase their growth is inhibited by penicillin transferred from the wound to the culture medium. It has a further use in the growth of blood cultures from patients receiving penicillin treatment, and in sterility tests on the drug.

Laboratory Methods.

Many and varied are the methods described for the qualitative or quantitative estimation of penicillin.[4] [16] [17] [18] All are a measure of the concentration of penicillin required to inhibit a standard organism. To determine the amount of penicillin in a sample of fluid, the extent of inhibition of the standard organism by the fluid is compared with the inhibition of the same organism produced by known quantities of penicillin. Essential requirements are therefore subcultures of standard organisms and accurately assayed samples of penicillin.

Standard Organisms.

Staphylococcus Aureus. In their original work the Oxford team used a strain of *Staphylococcus aureus* isolated by Heatley. Subcultures of this strain are used throughout England and America in the assays associated with the manufacture of penicillin, so that results are comparable. We have used an American strain designated *Staphylococcus aureus* N.R.R.L. 313, which gives results similar to those given by *Staphylococcus aureus* H.

Streptococcus. In his description of a method for penicillin assay of body fluids Rammelkamp[17] used a Group A β-hæmolytic streptococcus which was found to be inhibited repeatedly by 0·0078 unit per cubic centimetre of penicillin. We have used a subculture of this organism in assaying body fluids, because lower concentrations are detectable than when the less sensitive staphylococcus is used.

Both organisms were subcultured in nutrient broth each day. A 1 in 100,000 dilution in broth of a twenty-four-hour culture of the required organism was prepared for use in the tests. In this dilution (approximately 10,000 organisms per cubic centimetre) rapid growth occurs, ensuring maximum penicillin effect. Variations of the inoculum of between 1,000 and 100,000 do not affect the results.

Penicillin Standard.

In all tests a solution of penicillin of accurately determined concentration is required. We have been supplied with ampoules of the calcium salt containing exactly 330 units. This salt was dissolved in an accurately measured volume of buffer solution to make a strength of 12 units per cubic centimetre, which was

distributed in a number of small test tubes, and these were stored at 0° C. Buffer solution is prepared by dissolving eight grammes of sodium phosphate (Na_2HPO_4) and two grammes of sodium biphosphate (NaH_2PO_4) in one litre of distilled water, the resulting pH being 6·5 to 7·0.

For general purposes, results of sufficient accuracy can be obtained by using a sample taken from a therapeutic ampoule of penicillin of recent manufacture.

Estimation of Sensitivity of Bacteria.

The organism is isolated and an 18 to 24 hours broth culture prepared. Veal infusion broth (pH 7·4) containing 1% peptone and 0·5% sodium chloride was used; 10% normal horse serum was added if difficulty was experienced with such organisms as pneumococci or slow-growing streptococci.

Quantitative Estimation. A sample of the culture is diluted in broth 1 in 100,000 and the resulting broth suspension is distributed in a series of up to twelve small test tubes three inches by three-eighths of an inch, 1·0 cubic centimetre being placed in the first tube and 0·5 cubic centimetre in each of the others; 0·5 cubic centimetre of standard penicillin solution is added to the first tube. After the solutions are mixed, 0·5 cubic centimetre of fluid is transferred to the second tube and a similar amount to the third, and so on to the last tube, from which 0·5 cubic centimetre is discarded. As a result of these serial dilutions the penicillin content in each tube is as follows:

Tube 1	4·0 units per cubic centimetre.
Tube 2	2·0 units per cubic centimetre.
Tube 3	1·0 unit per cubic centimetre.
Tube 4	0·5 unit per cubic centimetre.
Tube 5	0·25 unit per cubic centimetre.
Tube 6	0·125 unit per cubic centimetre.
Tube 7	0·062 unit per cubic centimetre.
Tube 8	0·031 unit per cubic centimetre.
Tube 9	0·0156 unit per cubic centimetre.
Tube 10	0·0078 unit per cubic centimetre.
Tube 11	0·0039 unit per cubic centimetre.
Tube 12	0·0019 unit per cubic centimetre.

The tubes are incubated at 37° C. overnight, after which the broth in those tubes containing sufficient penicillin to inhibit growth is clear, whereas in the remainder it has become turbid as a result of bacterial multiplication. If, say, tubes 1 to 7 remain clear and tubes 8 to 12 are turbid, the result is read as "This organism is inhibited by 0·06 unit per cubic centimetre". While the result is given as a single figure, the true end point is somewhere between 0·06 and 0·03. The results of sensitivity tests on bacteria isolated from 143 cases are shown in Table III.

Qualitative Estimation. The following test determines whether an organism is sensitive or insensitive, and the degree of sensitivity can be roughly estimated.

A section of a blood agar plate is replaced by plain agar containing four units of penicillin per cubic centimetre (Figure III). Bacteria from a broth culture are seeded across the plate at right angles to the junction of the two agars. Owing to the fact that penicillin diffuses into the blood agar, sensitive organisms grow only at a distance from the agar junction depending upon the degree of their sensitiveness. Insensitive bacteria grow throughout the length of the seeded area and will even spread on to the plain agar. Cultures of a number of bacteria can be tested on a single plate. Pus or wound swabs may be streaked across this type of plate in order to identify the infecting organism and to obtain an estimate of its sensitivity. Delay is thus avoided, but the procedure will be successful only if sensitive bacteria are not overgrown by insensitive ones, and if no penicillin-destroying bacteria are present.

Methods of Assay.

Oxford Method.

The Oxford test is used for assay of the penicillin content of various fluids, and is the one generally used in assays associated with manufacture of penicillin. Fluids, for example pus, serum, serous exudates, which are not sterile, may also be assayed. Nutrient agar (pH 6 to 8) is poured into a series of Petri dishes to a depth of 3·0 to 5·0 millimetres. The surface of the agar is seeded by allowing a broth culture of the standard staphylococcus to flow over the surface, the excess being poured off. The plates are dried by incubation for one hour at 37° C., the lid being raised one-half of an inch. They may be stored for twenty-four hours at 0° C.

Small glass cylinders (9·6 millimetres high and 5·1 millimetres internal diameter) are placed upright on the surface of the agar and filled with the solution to be assayed. Penicillin diffuses into the agar and after incubation a zone of inhibition of growth is apparent around each glass cup, varying in diameter with the concentration of penicillin originally in the cup (Figure IV). The greatest variation in diameter has been found to occur when the concentration of penicillin is between 0·5 and 2·0 units per cubic centimetre, so that the greatest accuracy is obtained when solutions within these limits are used. A solution containing one unit per cubic centimetre gives a zone of inhibition 24 to 28 millimetres in diameter, depending upon the conditions of the test.

To determine the strength of a penicillin-containing solution, a number of dilutions are made to bring its estimated strength to about one unit per cubic centimetre. Four of the six cups are filled with these various solutions, the remaining two cups being filled with standard penicillin solution containing one unit per cubic centimetre. When the zone of inhibition produced by one of the dilutions of the unknown solution equals that produced by the standards, the strength of the unknown is easily calculated.

This method produces results which are accurate to within ±25%. Modifications of it are said to be more accurate.[16]

Serial Dilution Method.

In selecting a test for assay of body fluids, we have been influenced by the fact that smaller amounts of penicillin can be detected by a serial dilution test than by the Oxford assay or its modifications, although some degree of accuracy is sacrificed. The test is a modification of that described by Rammelkamp,[17] and when his strain of streptococcus is used, concentrations of penicillin as low as 1/128 unit per cubic centimetre are detectable. The test has proved satisfactory in the assay of serum, urine, cerebro-spinal fluid and serous exudates. All fluids which are not sterile must be Seitz-filtered.

Body fluids show varying degrees of turbidity which would interfere with the determination of the degree of bacterial growth. To overcome this disadvantage 1% by volume of washed erythrocytes is added to the broth suspension of the streptococcus. By this means, hæmolysis is the indicator of bacterial growth instead of turbidity, with equally accurate results.

Technique. One series of tubes (three inches by three-eighths of an inch) is set up containing the broth suspension of the standard hæmolytic streptococcus with red cells and serial dilutions of standard solutions of penicillin (12 units per cubic centimetre). This is known as the "standard" and is essentially a control of the sensitivity of the organism.

TABLE III.

Sensitivity Analysis of Clinical Strains Isolated.

Type of Organism Tested.	Number of Organisms Tested.	Units per Cubic Centimetre of Penicillin Required for Complete Inhibition of Growth.										
		4·0	2·0	1·0	0·5	0·25	0·125	0·06	0·03	0·0156	0·0078	0·0039
Staphylococcus	104	1			10	23	16	29	21	4		
Streptococcus—												
β hæmolytic	33						2	7	10	6	7	1
α hæmolytic	4	1				2			1			
Pneumococcus	5									3	1	1
Clostridium welchii	1									1		

A second series of tubes contains the same broth-organism-erythrocyte suspension in which serial dilutions of the sterile solution are made. (See Table IV.)

Figure V illustrates the result after incubation overnight. In the standard, the streptococcus has grown and produced hæmolysis in tubes 11 and 12, whereas no growth has occurred in tubes 1 to 10. Therefore 0·0078 unit of penicillin per cubic centimetre is the lowest concentration required to inhibit its growth. In the first serum, collected fifteen minutes after an injection of 10,000 units of penicillin, the highest dilution which has inhibited growth is 1 : 6, in tube 4. On the assumption that this tube will also contain 0·0078 unit of penicillin per cubic centimetre, the concentration in the undiluted serum is 6 × 0·0078, or 0·046 unit per cubic centimetre.

PHARMACOLOGY.

Methods of Administration.

On account of its extraordinarily low level of toxicity penicillin can be administered to patients by any known method. It is a great misfortune that the oral and rectal routes are useless—the penicillin is rapidly destroyed by the gastric acidity if given by the former method, and by penicillinase-producing bacteria if by the latter.[19] [20] Infants secrete little or no hydrochloric acid, so that penicillin could be given to them by mouth, and one case in which an infant was treated successfully has been recorded,[4] but further investigation is required before oral administration to infants can be recommended in all cases. If given into the duodenum through a duodenal tube, penicillin is absorbed and can be detected in the blood stream,[20] but large quantities would have to be used.

Because these methods are unsatisfactory, parenteral routes have to be used.

The Subcutaneous Route.

Given subcutaneously, penicillin is slowly absorbed with low levels in the blood stream.[20] Redness and swelling, with pain, occur around the injection site. In one series of reported cases treatment was carried out by continuous subcutaneous infusion, but constant watch for reaction is necessary and the site of injection requires frequent change.[21]

The Intramuscular Route.

Technically, the intramuscular method is the simplest, and clinical results are as satisfactory as with any other. When the drug is given with a fine needle of 24 to 26 S.W.G., the pain of the puncture is minimal and of the injection slight. The sodium salt, in concentration of 5,000 units per cubic centimetre, causes a stinging, burning pain of mild degree, which lasts for two to five minutes. No significant difference is detectable when stronger or weaker concentrations are used. The "refined" calcium salt causes even less discomfort than the sodium salt, but the crude calcium salt has to be diluted to concentrations as low as 2,000 units per cubic centimetre because intense pain, lasting up to fifteen minutes, results from stronger solutions.

To determine the rate of absorption of penicillin and its levels in the blood stream a number of patients have been investigated by the following method. Six to eight cubic centimetres of blood are withdrawn from a cubital vein and allowed to clot. The serum is used as a control. Penicillin is injected intramuscularly, and blood is collected at fifteen-minute intervals thereafter. All specimens are kept at ice-box temperature until assayed by the serial dilution method (Table IV, Figure V). Serum only is assayed because it has been proved that 90% of the total concentration in whole blood is contained in the serum.[20] From the results of the assay the penicillin levels are plotted as a graph (Figure V).

Figure VI illustrates the curves of serum levels found in three patients, after a single injection of 10,000 units of sodium salt, in three patients receiving "crude" calcium salt and three patients receiving "refined" calcium salt. It will be seen that penicillin is rapidly absorbed, a quick initial rise in concentration being produced, followed by a gradual fall. The "crude" calcium rises to a higher level and falls more slowly than the sodium salt, while the "refined" calcium salt is intermediate. The level to which penicillin rises and the length of time during which it is detectable in the blood stream show wide variation in different individuals. Although the graph shows a zero level after one to two hours, this means only that no penicillin was detectable by the method employed, and not that it was absent. It may be assumed that penicillin is present in the blood after this period, because it continues to be excreted in the urine and

TABLE IV.

Serial Dilution Method of Assay: Arrangement of Tubes and Contents for Routine Assay of Serum.

Amounts shown in Cubic Centimetres.

Standard.

Tube number	1	2	3	4	5	6	7	8	9	10	11	12	Control.
Broth containing 10,000 streptococci per cubic centimetre and 1% erythrocytes	1·0	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5
Standard solution of penicillin containing 12 units per cubic centimetre	0·5	—	—	—	—	—	—	—	—	—	—	—	—

Transfer 0·5 cubic centimetre serially from Tube 1 through each tube to Tube 12.

Final concentration of penicillin in units per cubic centimetre	4·0	2·0	1·0	0·5	0·25	0·12	0·06	0·03	0·015	0·007	0·003	0·001	—

Unknown Solution.

Tube number	1	2	3	4	5	6	7	8	9	10	11	12	Control.
Broth containing 10,000 streptococci per cubic centimetre and 1% erythrocytes	0·1	0·5	1·0	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·1
Unknown solution, for example serum, urine *et cetera*	1·0	0·5	0·5	—	—	—	—	—	—	—	—	—	—

Transfer 0·5 cubic centimetre serially from Tube 3 through each tube to Tube 12.

Dilution of unknown so produced	1 : 1	1 : 2	1 : 3	1 : 6	1 : 12	1 : 24	1 : 48	1 : 96	1 : 192	1 : 384	1 : 768	1 : 1536	—
Control serum	—	—	—	—	—	—	—	—	—	—	—	—	1·0

because streptococci grown in the serum show morphological changes illustrated in Figure II.

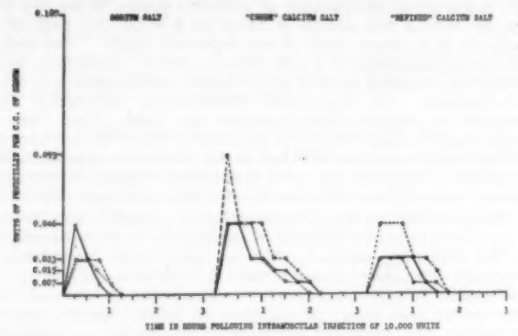

FIGURE VI.
Serum levels following a single intramuscular injection of 10,000 units of penicillin.

From Figures VII, VIII and IX it will be seen that with each increase in the amount of penicillin injected, a higher level is attained and the drug is detectable for a longer period. Assay carried out after the administration of 40,000 units and 50,000

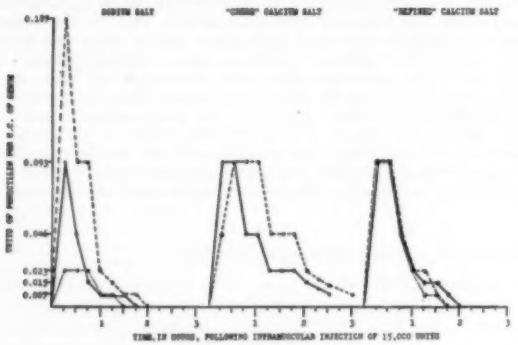

FIGURE VII.
Serum levels following a single intramuscular injection of 15,000 units of penicillin.

units showed no significant advantage over 30,000 units. The level reached was no higher, and penicillin could not be detected for any longer time.

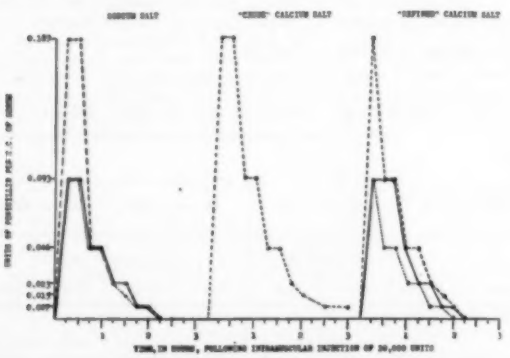

FIGURE VIII.
Serum levels following a single intramuscular injection of 20,000 units of penicillin.

Because penicillin cannot be detected in serum after two to three hours, most writers recommend that the drug should be given at intervals of three hours, or if smaller doses are used, at intervals of two hours. The excellent results obtained by giving penicillin intramuscularly at intervals of three hours have confirmed this idea. No difference could be detected in serum level curves after the first injection or after the tenth injection

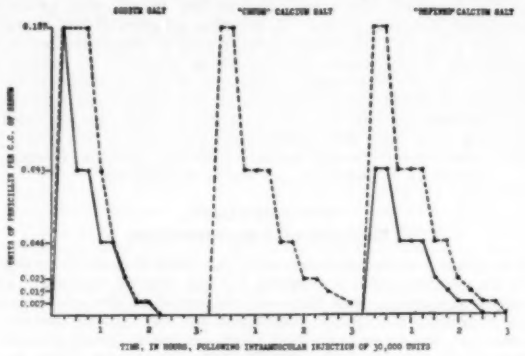

FIGURE IX.
Serum levels following a single intramuscular injection of 30,000 units of penicillin.

at intervals of three hours during a course of treatment Cumulative effect is thus excluded with this routine. The great disadvantage of this system is that the patients' sleep is disturbed because the injections have to be continued day and night.

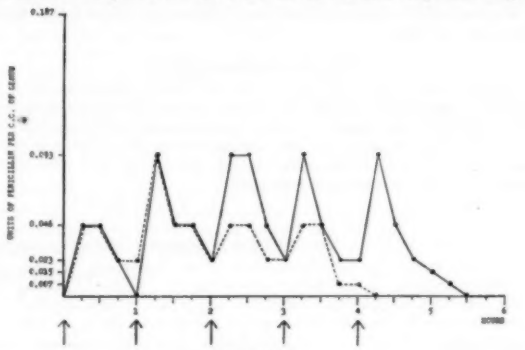

FIGURE X.
Cumulative effect in two cases resulting from hourly intramuscular injections of 10,000 units of sodium penicillin.

After a few days this becomes distressing. To avoid this we have devised an alternative routine, with which sleep is not disturbed and from which equally good results have been

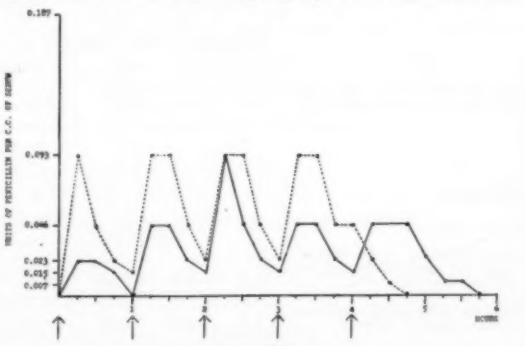

FIGURE XI.
Cumulative effect in two cases resulting from hourly intramuscular injections of 10,000 units of "refined" calcium penicillin.

obtained. Four or five injections are given at intervals of one hour, twice daily, convenient times being at six, seven, eight, nine and ten o'clock morning and evening. Figure X

shows the serum levels obtained in two cases when this method was used with 10,000-unit doses of sodium penicillin and Figure XI the levels obtained with "refined" calcium penicillin.

It will be seen that a cumulative effect is obtained and that penicillin is detectable in a patient's serum for almost six hours. Morphological changes in streptococci (Figure II) have been detected when grown in serum collected two and a half hours after penicillin was undetectable by the assay method. Thus with 10,000 unit doses given by this "cumulative" method, penicillin effect is present in a patient's serum for up to seventeen

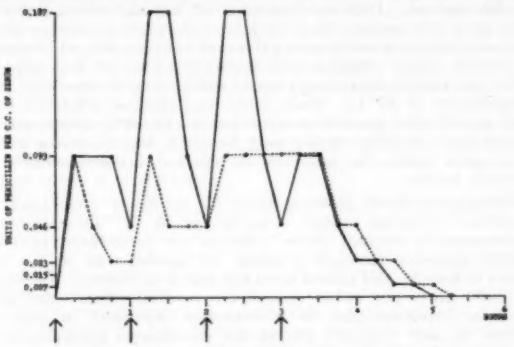

FIGURE XII.

Sodium penicillin 20,000 units dose. Serum levels in two cases following repeated intramuscular injections at hourly intervals.

hours per day, with a total daily dosage of 100,000 units. Larger amounts—15,000 or 20,000 units—give longer "penicillin effect" and higher levels. It should not be necessary to give more than 20,000 units for each injection.

Penicillin has been given by continuous intramuscular infusion, but the method is liable to be associated with intramuscular abscess formation.[22]

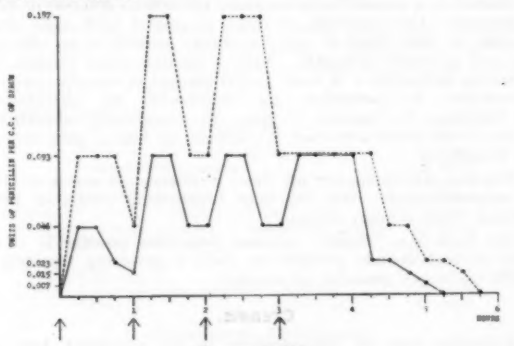

FIGURE XIII.

"Refined" calcium penicillin 20,000 units dose. Serum levels in two cases following repeated intramuscular injections at hourly intervals.

The Intravenous Route.

Penicillin can be given intravenously by intermittent injection or as a continuous drip infusion.

In the investigation of serum levels, blood was collected from patients at five minutes, ten minutes and fifteen minutes after the injection and thereafter at fifteen-minute intervals. The graphs show a very rapid rise and fall, and a high level of short duration. As a result, it is felt that this method has no advantages over intramuscular injection, and has not been used in treatment.

Serum assays made twice a day in the case of three patients receiving 200,000 units of penicillin per day by continuous intravenous infusion reveal that a constant level of between 0·023 and 0·046 unit is maintained; when 100,000 units are given, penicillin is detectable only occasionally and then in a concentration of 0·007 to 0·015 unit. These are low levels, but excellent clinical improvement results. Herrell[23] gives 40,000 to 60,000 units of either sodium or calcium salts by this method and reports very good results.

The method has serious disadvantages: (i) With concentrations of 250 units per cubic centimetre phlebitis was of an alarming degree in two of our patients. With concentrations of 50 to 100 units per cubic centimetre it still occurs frequently and daily change of the needle or cannula to a new site is necessary to avoid serious reaction. (ii) Four litres of saline solution containing 50 units per cubic centimetre, or two litres containing 100 units per cubic centimetre, are required for the administration of a total daily dose of 200,000 units. These large quantities incur the risk of "waterlogging" the patient, but if the intravenous administration of fluid, serum or blood is indicated, penicillin may be added to the infusion with advantage. (iii) Potency is decreased when penicillin is kept in solution at room temperature. A solution originally containing 100 units per cubic centimetre may contain only 70 or less at the end of twelve hours. Citrated blood and pooled human serum are compatible with penicillin, and little reduction in potency occurs in twelve hours at room temperature.

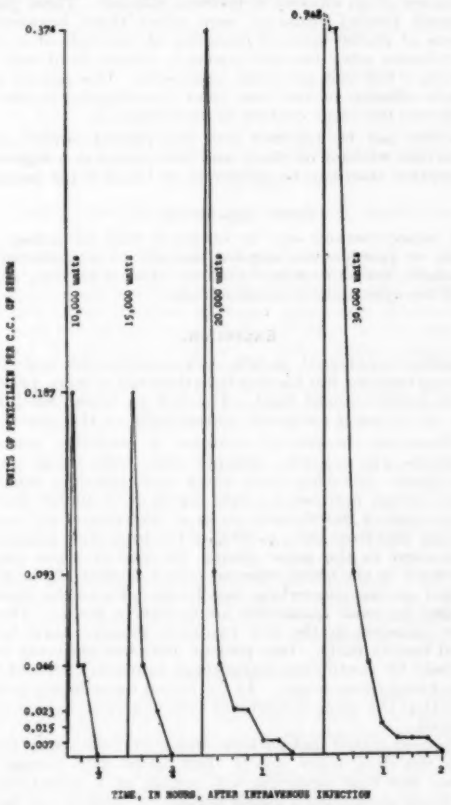

FIGURE XIV.

Serum levels after single intravenous injections of penicillin.

The Intrathecal Route.

Even when present in the blood in high concentrations, penicillin does not pass into the cerebro-spinal fluid. In the case of one patient who was receiving 200,000 units per day by continuous intravenous infusion, no penicillin was found in cerebro-spinal fluid removed by lumbar puncture. The same result was obtained in the case of two patients receiving 15,000 units by intramuscular injection every third hour.

Fortunately penicillin can be injected without risk into the spinal theca, into the *cisterna magna* or into the cerebral ventricles. Rammelkamp and Keefer[24] reported that intrathecal injections of 5,000 to 10,000 units of penicillin caused headache, rise of cerebro-spinal fluid pressure and rise of cell count. Such has not been our experience with Penicillin "Commonwealth", either sodium or "refined" calcium salts. Repeated injections of between 5,000 units and 15,000 units have been given to three patients. No immediate or delayed

sequelæ resulted; headache did not occur, and cell count remained stationary or progressively decreased.

After intrathecal injection, penicillin is detectable both in the blood stream and in the urine,[24] and it remains in the cerebro-spinal fluid in detectable amounts for a considerable period. One patient had 10,000 units of sodium penicillin injected into the right cerebral ventricle; 0·4 unit per cubic centimetre was found in fluid removed by lumbar puncture fourteen hours later. In the case of another patient, 1·5 to 3·0 units per cubic centimetre were repeatedly found in the cerebro-spinal fluid removed twenty-four hours after intrathecal injections of 15,000 units of "refined" calcium salt. In the cerebro-spinal fluid of two patients who were given 10,000 units and 15,000 units of sodium penicillin intrathecally, none was detected twenty-four hours after injection.

Injection into Serous Cavities.

Penicillin diffuses into the pleural cavity and joints, but in the presence of an effusion it becomes diluted. Three patients with small pleural effusions were given three intramuscular injections of 20,000 units of penicillin at intervals of an hour; thirty minutes after the last injection, pleural fluid was found to contain 0·023 unit per cubic centimetre. One patient with a traumatic effusion of the knee joint, investigated in the same way, showed this same content in the effusion.

Penicillin can be injected into the pleural cavity or into joint cavities without ill effect, and this results in a higher local concentration than can be produced by blood-borne penicillin.

Local Application.

High concentrations can be obtained with advantage when solutions or powders are applied directly to an infected area, for example, deep or surface wounds, abscess cavities, infected areas of the eyes, nose or nasal sinuses.

Excretion.

Penicillin is excreted in bile, saliva and urine and diffuses into serous cavities, but has not been detected in tears, pancreatic juice or cerebro-spinal fluid. The fall in blood level is due mainly to its rapid excretion, particularly in the urine.

To determine the rate of excretion of penicillin, urine from ten patients was assayed. Samples were collected at intervals of two hours following both single and multiple injections: the dose varied between a single injection of 10,000 units and five injections of 20,000 units given at intervals of an hour. It was found that from 20% to 50% of the total dose administered was excreted in the urine during the period when penicillin is detectable in the blood, whereas only a further 1% to 5% was recovered in the succeeding two hours. Excretion thereafter proceeded in small quantities up to twelve hours. The total amount excreted in the last two-hour period varied between one and twenty units. One patient, who was receiving 100,000 units daily by continuous intravenous infusion, excreted 49,000 units in twenty-four hours. In the period immediately following an injection the urine is coloured yellow and an active diuresis is induced.

It has been stated that patients with diminished renal function excrete the drug more slowly than those with normal renal function, and that penicillin will remain at a detectable level in the blood stream for a longer period.[20] One of our patients, with chronic nephritis, who had generalized œdema and a blood urea content of 100 milligrammes *per centum*, was given 10,000 units of "refined" calcium salt intramuscularly. The serum level did not rise higher than would be expected in a normal individual, but penicillin was detectable for a period of one and three-quarter hours, which is thirty minutes longer than in normal cases in our series.

Preparation for Use.

In the preparation of solutions, powders, ointments *et cetera* it must be borne in mind that penicillin is not a general antiseptic; although it kills many pathogenic bacteria, others will grow freely in its presence and would be a danger to the patient. English writers report a death caused by *Bacillus pyocyaneus* septicæmia, following continuous intravenous administration of penicillin, the focus of infection being at the site of infusion.[23]

Air-borne as well as pathogenic bacteria are capable of destroying penicillin. It is stressed, therefore, that strict asepsis must be maintained both in the preparation of the drug for use and in its administration to the patient.

The physical properties of penicillin being borne in mind, all preparations, whether in ampoules, powders or solutions, must be kept in a refrigerator or ice-chest, and should never be allowed to come in contact with antiseptics, particularly those containing spirit. Syringes, needles, rubber tubing should all be boiled in water of neutral reaction, and not sterilized by antiseptics.

Solutions.

"Soluvac" saline and other solutions were examined that their pH and their destructive effect on penicillin potency might be determined. Different samples of normal saline solution were at a pH ranging from 6·7 to 7·8, whereas the range of glucose solutions was between pH 4 and 5. Up to 40% of penicillin in normal saline solution was destroyed when it was kept at 24° C. for twelve hours, and up to 60% when it was kept at a temperature of 37° C. Tests when the glucose solutions were used as solvents showed destruction up to 90% under similar conditions. Distilled water may be used, but it causes rather more pain when the solution is injected intramuscularly or instilled locally.

Throughout these investigations all solutions were made in "Soluvac" normal saline solution at 5° C. Twenty cubic centimetres of normal saline solution are introduced into the opened ampoule through a gauge 15 needle, four and a half inches in length, and mixed until the salt is dissolved; a solution of 5,000 units per cubic centimetre results. This solution is used for intramuscular or intravenous injection, or may be diluted to any required extent for continuous intravenous or local use. The "refined" calcium salt dissolves with even greater ease than the sodium salt. Solutions were transferred from the ampoule to bottles with vaccine type rubber stopper from which they were removed aseptically as required. This solution of 5,000 units per cubic centimetre is added to flasks of normal saline solution, pooled human serum or blood, to make a final concentration of 50 to 100 units per cubic centimetre for use as a continuous intravenous infusion.

Powder.

It would be extremely wasteful to apply penicillin powder undiluted to a wound, as it contains 150,000 to 400,000 units in a gramme. Consequently, it must be mixed with some other powder in order that it may be evenly spread in an effective but not wasteful strength. Such a diluent must possess the following properties: it must be (*a*) neutral in reaction and not destructive to penicillin, (*b*) sterilizable by autoclaving, (*c*) harmless to human tissues, (*d*) completely absorbable, (*e*) non-toxic when absorbed, (*f*) sufficiently fine to pass through an insufflator.

Powders which answer all these requirements are a mixture of sulphanilamide with 5% light magnesium oxide, or finely ground dried human serum.[25]

For local use "crude" calcium penicillin powder is mixed with sulphanilamide powder to yield a resulting strength of 5,000 units per gramme of powder.

Creams.

Penicillin can be incorporated in an ointment base for application to superficial lesions. The base must possess similar properties to those described for a powder. English writers recommend "Lanette Wax S.X.", "Vaseline" and water in equal parts.[25] This formula produces an oil-in-water emulsion with which solutions of penicillin are easily mixed. Penicillin incorporated in this base shows a rapid initial destruction of potency of about 30%, still further destruction occurring more slowly. The ointment must be used within four days of the mixing. After investigation of a number of ointments available in Australia, "Barrier Cream" (Faulding) has been found to be satisfactory, but clinical trials are as yet incomplete. A mixture of penicillin with this base in a strength of 250 units per gramme was kept at room temperature for seven days, at which time assay showed its strength to have fallen to 150 units per gramme. "Barrier Cream" may be sterilized by autoclaving, but when hot separates into its oil and water phases. The emulsion is easily reconstituted by shaking, as it cools. Penicillin is incorporated in the base, after sterilization, by stirring in a solution to give a final concentration of 250 to 1,000 units per gramme. Emulsions are used in preference to oil bases because they are easily and quickly washed off with water or saline solution, which should be carried out before each fresh application.

DOSAGE.

There is wide variation in doses recommended by different writers[19] [21] [22] [23] [26] [27] [28] because there are so many variable factors. In an acute spreading cellulitis in which the organism is dividing rapidly and there is an adequate blood supply to the infected area, therapy will be rapid in effect and need be of short duration. In chronic fibrosing lesions the organism is reproducing slowly and there is a poor blood supply, so larger doses are required and have to be continued for a longer period.

In our opinion, full effect can be obtained in adults with a total daily dose of 100,000 to 200,000 units, given parenterally. Any greater amount is wasteful. Although no children or infants have been treated, we consider that they should receive correspondingly lower doses, although body weight is not the only factor which influences the serum levels obtained after injections of penicillin.

No useful purpose is served by commencing with a large dose, because the drug is excreted almost as rapidly as when smaller doses are given and no "build-up" is attained, as occurs with drugs more slowly excreted.

The intramuscular route seems to us to be the most suitable method. Equally good results are obtained either by the routine administration of 10,000 to 20,000 units given at intervals of three hours, or by the "cumulative" routine administration of 10,000 to 15,000 units at six, seven, eight, nine and ten o'clock morning and evening.

Continuous intravenous administration of between 100,000 and 200,000 units per day is just as effective, but the method has its disadvantages and its dangers. However, if infusions of saline solution, serum or blood are indicated penicillin may be added with advantage.

The duration of penicillin therapy and the total dose must depend upon (*a*) the type of infection, whether acute or chronic; (*b*) the nature of the infecting organism; (*c*) the clinical response. In chronic infections it must be remembered that although many organisms are killed, others may remain latent, only to develop again immediately therapy is ceased. It is advisable therefore to continue administration for some days after the lesion has subsided.

RESULTS OF CLINICAL TRIAL.

One hundred and forty-one patients have been treated by various methods, with both sodium and "refined" calcium salts. The use of "crude" calcium salt was confined to local therapy. The treatment was as follows:

Sodium penicillin—	
Continuous intravenous injection	8 cases
Intramuscular injection:	
Three or four hourly routine	42 cases
"Cumulative" routine	50 cases
Intrathecal injection	3 cases
Intrapleural injection	1 case
"Refined" calcium penicillin—	
Intramuscular injection—"cumulative" routine	29 cases
Intrathecal injection	1 case
"Crude" calcium salt—	
Local therapy:	
Combined with parenteral therapy ..	32 cases
Alone	20 cases

Parenteral Treatment.

Administration by injection, either intramuscular or intravenous, is required when the active principle can be brought into contact with the infecting organisms by the blood stream only. It has been used in the following conditions.

Lobar Pneumonia.

Five patients with lobar pneumonia were treated as shown in Table V.

All were acutely ill and treatment was commenced within twenty-four to thirty-six hours of the onset of illness. Response to treatment was dramatic and within twenty-four to thirty-six hours fever had subsided (Figure XV) and all were comfortable, eating and sleeping well.

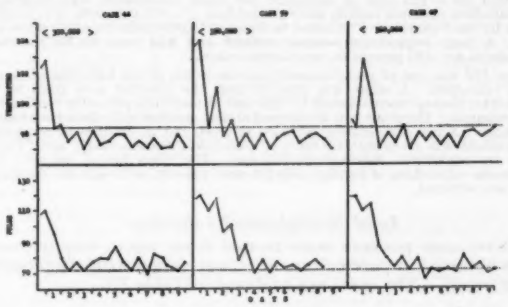

FIGURE XV.
Temperature charts in three cases of pneumonia.

Clinical signs of consolidation were not typical in all cases. Tubular breathing was detected in two cases and in the other three the findings were little more than some impairment of the percussion note, increase in vocal resonance, diminished air entry and occasional crepitations. Within a few days these abnormal signs had vanished. Daily X-ray examinations were made. The film taken after twenty-four hours of treatment usually showed some extension of the consolidation seen in the film taken before treatment was commenced. Thereafter the opacity gradually disappeared over a period of seven to ten days.

White blood cell counts were made daily in four cases; in two the count rose after twenty-four hours of treatment and then returned to normal, one in two days and the other in ten. In this latter case a small amount of sterile fibrino-purulent fluid was aspirated from the pleural cavity on the third day. This effusion resolved without further treatment. In the other two cases the count was normal on the third day. In Case 77 fever recurred on the fifth day and treatment was continued despite clinical and radiological evidence of resolution. This fever was subsequently proved to be malarial in origin.

Osteomyelitis.

One patient with acute osteomyelitis and three with acute exacerbation of a chronic osteomyelitis have been treated by this method. In all cases the infecting organism was found to be hæmolytic *Staphylococcus aureus* and the infection was rapidly controlled without resort to surgery, although one patient developed a small sinus which has since healed.

TABLE V.
Investigations in Five Cases of Pneumonia.

Case Number.	Pneumococcus.		Investigation.		Units of Penicillin Given.
	Type.	Sensitivity. (Units per Cubic Centimetre.)	Site of Consolidation Seen on X-ray Examination.	Initial White Blood Cells per Cubic Centimetre).	
77	XXVII	0·0156	Right lower lobe.	29,000	1,040,000
44	Not determined	0·0078	Lower half of left lower lobe.	27,100	300,000
47	XI	0·0156	Lower half of left lower lobe.	17,700	360,000
53	IV	0·0156	Right lower lobe.	Not determined	300,000
59	I	0·0039	Right base.	20,600	350,000

Case 109 was one of recurrent osteomyelitis of the left humerus. The original infection occurred twenty-two years ago. The left arm was swollen, reddened and extremely painful. X-ray examination revealed cortical sclerosis, but no sequestra or cavities. Penicillin was given in doses of 20,000 units every three hours for ten days, a total of 1,600,000 units. Symptoms and signs subsided rapidly after the first forty-eight hours (Figure XVI), but a small amount of purulent fluid escaped through an area where the skin sloughed. Culture yielded hæmolytic *Staphylococcus aureus* inhibited by 0·25 unit of penicillin per cubic centimetre. The sinus healed in six weeks (Figure XVI).

Case 10 was one of osteomyelitis of the left radius. An abscess of the left forearm of three weeks' duration was incised in two places. X-ray examination of the forearm revealed no bony pathological change. The inflammation did not subside and after a further three weeks X-ray examination revealed extensive osteomyelitis of the radius. Hæmolytic *Staphylococcus aureus*, inhibited by 0·125 unit of penicillin per cubic centimetre, was recovered. The infection subsided rapidly after a total dose of 1,100,000 units of penicillin, given by the "cumulative" routine in doses of 15,000 units for eight doses per day. A large sequestrum became evident and will have to be removed. Organisms are still present in an unhealed sinus.

Case 122 was one of post-traumatic osteomyelitis of the left tibia of eleven years' duration. A sinus was present over the infected area from which hæmolytic *Staphylococcus aureus* (0·125 unit of penicillin per cubic centimetre) was cultured. The sinus had discharged almost continuously since the original infection. X-ray examination revealed sclerosis but no cavities or sequestra. The patient was given 800,000 units of penicillin intramuscularly and 275,000 units by continuous intravenous infusion. The sinus healed rapidly, but five weeks later signs of further activity were present, although the discharge had not recurred.

Local Staphylococcal Infections.

Thirty-nine patients were treated from whom staphylococci were obtained in pure culture or in association with streptococci (four cases). The cases are analysed in Table VI.

TABLE VI.

Results of Treatment in Superficial Staphylococcal Infections.

Type of Condition.	Number of Cases.	Results.	
Carbuncles	10	Rapid response	7
		Slow response	2
		Unaffected	1
Recurrent furunculosis.	20	Immediate response	12
		Known recurrence	8
Impetigo type lesions	4	Rapid response	4
Infected fingers ..	5	Rapid response	2
		Slow response	3
		(Osteomyelitis present, 2)	

All patients were treated with intramuscular injection. In the majority relief of pain was outstanding and healing was rapid. The improvement was most marked in acute cases and single acute carbuncles resolved extremely rapidly with little necrosis. Streptococci, when present, disappeared, but staphylococci could be cultured from the area throughout treatment until healing was complete. The presence of these latter organisms did not appear to delay healing.

In chronic cases, particularly cases of recurrent furuncle, fresh lesions responded like other acute infections, but in eight cases further boils appeared either during penicillin therapy or shortly afterwards.

Case 110 was one of a large carbuncle in the middle of the back of fourteen days' duration. The area of necrosis was three inches in diameter surrounded by œdema and redness six inches in diameter. Pain was relieved overnight and temperature subsided (Figure XVI); the slough separated by the fifth day, leaving a clean granulating wound which healed in three weeks after skin grafting. Repeated cultures yielded hæmolytic *Staphylococcus aureus* inhibited by 0·015 unit of penicillin per cubic centimetre. The total penicillin given was 800,000 units of "refined" calcium salt.

Renal Tract Infections.

Infections of the renal tract caused by Gram-positive cocci or by gonococci are very susceptible to penicillin therapy. Not only is there a good blood supply to the infected areas, but a concentration as high as 96 units per cubic centimetre has been found in the urine. This concentration must certainly act as a form of local application.

Case 104 was one of recurrent acute cystitis with hæmaturia and gross dysuria, caused by hæmolytic *Staphylococcus aureus* inhibited by 0·125 unit of penicillin per cubic centimetre. Recurrence was present for twelve days before treatment was commenced. Penicillin was given by intramuscular injection, 15,000 units every three hours—a total of 600,000 units. Symptoms had completely subsided at the end of five days. Subsequent attempts at culture were fruitless; cystoscopy revealed a normal bladder.

Case 123 was one in which bilateral renal calculi were present with chronic staphylococcal pyelitis. After removal of calculi from the right kidney the patient developed an exacerbation of the pyelitis and a staphylococcal wound infection. "Refined" calcium penicillin was given, ten injections per day of 10,000 units by the "cumulative" routine—a total of 1,000,000 units. The temperature subsided after three days and the patient's general condition was much improved after 800,000 units. The wound healed, but organisms were still recoverable from the urine.

It is possible that the remaining calculus continued to be a source of infection.

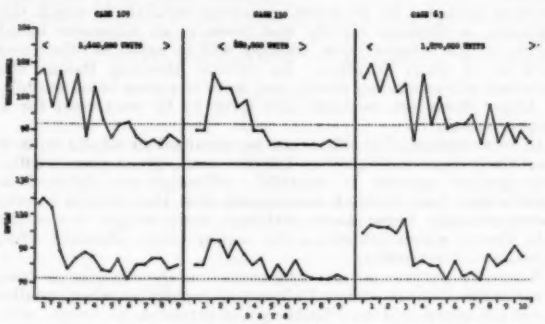

FIGURE XVI.

Temperature charts in three cases of staphylococcal infection treated with penicillin.

Combined Parenteral and Local Therapy.

Combined therapy is indicated in cases in which there is an area of infection to which penicillin can be applied locally, but in which such an area is associated with surrounding inflammation for which intramuscular injections are required.

Osteomyelitis.

The fourteen patients treated suffered either from chronic osteomyelitis associated with a discharging sinus or from osteomyelitis associated with compound fractures due to gun-shot wounds. Five patients were febrile and "toxic", and penicillin therapy brought about great improvement in their general condition, thus permitting subsequent operation to be carried out with reduced risk. Local treatment, combined with the parenteral treatment, was continued for prolonged periods both before and after operation. In these conditions it is as yet impossible to judge just how completely penicillin has succeeded in defeating the bone sepsis. However, the general clinical improvement which is obtained soon after therapy is commenced and which persists for variable periods after it is completed, leads to greatly improved appetite with increased protein intake, long periods of restful sleep and reduction in pain, and in general, the patient is put into a much better condition to combat his infection and to withstand operative procedures. After operation the convalescence has been uniformly uneventful and marked by rapid and continued improvement. Wound reaction has been minimal with an almost complete absence of redness or swelling. Most wounds were loosely sutured with or without a small drain tube, and a penicillin tube was inserted into the depths of the cavity. Drainage tubes were removed early, as soon as the blood-stained oozing from bone had ceased, as their presence also allowed the penicillin to escape. Subsequently, the thin discharge decreased and, if all sequestra had been removed, the wound healed in its entirety. With no dead bone remaining, pathogenic organisms were rarely recovered from the discharge.

Case 63 was one of gun-shot wound of both legs with compound fracture of the left femur. Eight months later sequestration was present along the shaft of the femur with some bony union. Hæmolytic *Staphylococcus aureus* had been isolated from the wound on a number of occasions. An acute exacerbation of infection occurred with fever to 102° F. and considerable induration of the whole thigh. Culture yielded green zoned streptococci inhibited by 0·03 unit of penicillin per cubic centimetre and hæmolytic streptococci inhibited by 0·0078 unit per cubic centimetre. Penicillin therapy was commenced with 15,000 units given intramuscularly every three hours (120,000 units per day). After one week of treatment temperature and pulse were normal (see Figure XVI), discharge had diminished in quantity, induration had considerably lessened and the general condition of the patient, who previously had been "toxic" and querulous, was now greatly improved physically and mentally. Culture yielded *Bacillus proteus* only. Sequestrectomy was performed on the eleventh day of treatment, the sequestra being removed through preexisting medial and lateral sinuses which were enlarged. The wounds were loosely sutured with one penicillin tube in each. Slight fever to 100° persisted for five days following operation. Parenteral administration ceased two days after operation, the total dose having been 1,840,000 units. Penicillin was instilled locally for fourteen days and tubes were removed. Cultures from wounds following operation repeatedly contained *Bacillus proteus* and *Bacillus pyocyaneus* only. One month after operation the lateral sinus was healed, and the medial wound had a minimal discharge and was almost healed.

Case 92 was one of gun-shot wound of the right shoulder and arm with comminuted fracture of the upper third of the right humerus and the outer third of the right clavicle with radial nerve paralysis. Gross sepsis

persisted for the following two months with nephritis, raised blood pressure, œdema and albuminuria. After two months sequestrectomy was performed and six sequestra were removed. Further high fever occurred for another five weeks, the temperature rising to 104° F. With each exacerbation of fever hæmaturia and albuminuria occurred. At this stage, three months after the infliction of the wound, 1,000,000 units of penicillin were given by intramuscular injection over six days, with diminution in temperature, lessening of discharge and considerable improvement generally. In repeated wound cultures *Bacillus proteus* only was grown. After more adequate immobilization in a plaster shoulder spica, improvement was maintained, but further loculation of pus led to rise in temperature, pain and toxic hepatitis with deep jaundice. Penicillin was recommenced intramuscularly, 10,000 units every three hours (80,000 units daily) for ten days, with some general improvement but little diminution in fever or jaundice. Discharge from the wound was now very copious; *Bacillus proteus* and *Bacillus coli* were present. Five weeks after jaundice appeared it had gradually disappeared and sequestrectomy was performed, one drain tube and one penicillin tube being inserted in the wound. Culture after operation revealed some Gram-positive staphylococci as well as *Bacillus proteus* and *Bacillus coli*. Marked improvement occurred subsequently. After a further three weeks a small hypostatic abscess was incised in the posterior wall of the axilla. Examination through the abscess cavity revealed that there was still present some dead bone which had not separated sufficiently for removal.

Case 33 was one of gun-shot wound of the left inguinal region with comminuted fracture of the pubes, exposure of cord and herniation of the bladder into the wound. This was succeeded by osteomyelitis of the ischio-pubic rami, involving the pubic symphysis with high fever, anæmia and a severe degree of toxæmia. No response followed courses of sulphapyridine, sulphathiazole and anti-malarial treatment. Numerous abscesses formed and were incised through the buttock, in the inguinal region and in the medial aspects of both thighs. Five months after receipt of the wound penicillin was given intramuscularly, 20,000 units every three hours (160,000 units a day) for six days, with some general and little local improvement. Six months after being wounded the patient was very emaciated and "toxic", five sinuses discharging; hæmolytic *Staphylococcus aureus* was isolated from the pus. Persistent pain occurred in the pubic region. All sinuses were injected with calcium penicillin solution (250 units per cubic centimetre) for three and a half weeks. Much local improvement followed, with disappearance of pain and lessening of discharge and some general improvement, but fever persisted. Then the patient was given five litres of pooled human serum intravenously over three days, each litre containing 200,000 units of penicillin, a total dose of 1,000,000 units. Marked general improvement followed, with much improved appetite, some gain in weight, no pain and very slight discharge from the sinus. *Bacillus proteus* and *Bacillus pyocyaneus* were recovered in culture. X-ray examination revealed considerable repair. Over the following month the patient's condition gradually relapsed with increase in fever and toxæmia. Eight and a half months after infliction of the wound exploratory operation was performed, one small sequestrum was removed and the retropubic region and the old sinuses were found to be filled with grey, indolent granulation tissue. Two penicillin tubes and two drain tubes were inserted and penicillin was instilled for a further two weeks. The patient's condition remains unchanged.

In Case 33 little success has been achieved, and this is attributable to the fact that there was chronic osteomyelitis in cancellous bone, some of which was beyond the reach of penicillin given locally and generally. With each course of treatment good clinical improvement occurred only to be succeeded by a relapse.

Case 101 was one of bomb wound of the right buttock with fracture of the ilium in the region of the sacro-iliac joint. Six and a half months after being wounded the patient was well, was walking, and had good hip movement, but a sinus was present in the right buttock through the healed wound. A culture of *Staphylococcus aureus* was obtained and was inhibited by four units of penicillin per cubic centimetre. The sinus was injected with calcium penicillin solution (250 units per cubic centimetre) twice daily for a week. The sinus healed. Two days later the sinus broke down and discharged a small flake sequestrum. A culture of hæmolytic *Staphylococcus aureus* was obtained. A further sequestrum was discharged two weeks later and after a further week the area was explored and several small sequestra were removed from a cavity in the body of the ilium. A flap graft of *gluteus maximus* was cut and inserted into the cavity. A penicillin tube led down to the base of the graft pedicle. Two days after operation the whole wound area was painful and inflamed, and hæmolytic *Staphylococcus aureus* was grown in culture. Five days after operation much pain, redness and induration occurred with fever to 100° F. Penicillin treatment was commenced, 20,000 units being given intramuscularly for five single hourly injections, morning and evening (200,000 units daily). The temperature rapidly subsided, and penicillin therapy was ceased after six days, the total dose having been 1,200,000 units. Three weeks after operation the patient was walking, and the wound and sinus were healed.

This patient had a general staphylococcal infection of the whole wound area following operation, the organism being comparatively resistant (four units per cubic centimetre). Local instillation was unable to control the infection, as owing to the very nature of the operation performed it was not possible to make the solution permeate the whole area. The addition of parenteral therapy caused fairly rapid subsidence.

Case 89 was one of dorsal dislocation of the left hip with a marginal fracture of the acetabulum. Open reduction was performed and the posterior lip of the acetabulum was replaced and secured with two nails. Three days after operation a hæmolytic *Staphylococcus aureus* infection was apparent. Considerable fever with profuse discharge occurred for the following three months. No improvement occurred with the use of sulphonamides or after removal of the nails five weeks after the original operation. At the end of three months penicillin therapy was commenced by continuous intravenous infusion, 200,000 units being given daily, and within forty-eight hours the temperature was normal. Infusion was stopped after seven days and the sinus was injected twice a day thereafter with calcium penicillin solution, 250 units per cubic centimetre. Hæmolytic *Staphylococcus aureus* was still recovered in culture. X-ray examination at this stage revealed extensive osteomyelitis of the head and neck of the femur with marked destruction of the joint and a recurrence of the dislocation. The dislocation was reduced again by means of skeletal traction, but four weeks after the cessation of penicillin therapy a further course of 120,000 units daily had to be given intramuscularly because of a recrudescence of infection. This course extended for a period of three weeks and a total of 2,440,000 units was given. Clinical response was much more delayed. At present the head of the femur is fixed in the acetabulum, but discharge still persists. X-ray examination shows great destruction of the head of the femur and acetabulum. No sequestra are visible. *Bacillus coli* and *Staphylococcus aureus* are recoverable in a culture.

It has apparently been impossible to bring penicillin into contact with all the areas of infection. When therapy is stopped, remaining organisms spread and cause recrudescence of infection.

Meningitis.

As penicillin is not secreted into the cerebro-spinal fluid, meningeal infections by sensitive organisms must be treated by intrathecal injection, but as so many meningeal infections are thought to be associated with a septicæmia and as organisms actually invade meninges and can be attacked there by blood-borne penicillin, it is advisable to combine intrathecal with intramuscular therapy. In infections by a sensitive organism which does not respond the possibility must be borne in mind that penicillin injected into the spinal theca may be prevented from diffusing upwards either by adhesions, or by a cerebro-spinal fluid thickened by the presence of numerous pus cells. In such cases it may be necessary to give penicillin by cisternal or even by ventricular puncture.

Case 69 was one of chronic mastoiditis, *otitis interna* and extradural abscess. When the patient presented for treatment, the mastoid process had been removed, the dura was exposed over a considerable area, the petrous temporal was deeply excavated with exenteration of the middle ear. The patient was febrile and very ill, with severe frontal headache, and extension of infection forwards around the zygoma. Streptococci (inhibited by 0·06 unit of penicillin per cubic centimetre) and staphylococci (inhibited by 0·25 unit per cubic centimetre) were obtained in a culture from the wound. Although the cerebro-spinal fluid was sterile, there were present 300 polymorphonuclear cells per cubic millimetre. Penicillin was given—800,000 units parenterally in four days, 10,000 units intrathecally, with instillations every two hours of solution containing 20 units per cubic centimetre. Thereafter the patient's condition became almost normal; the wound was healing, his temperature was normal, but he still complained of mild headache although no increase in cells was present in the cerebro-spinal fluid. Four weeks later he had a recurrence of symptoms and after a further course of penicillin, 1,600,000 units given intramuscularly in twelve days, the patient again became apparently normal. After a short interval symptoms and signs of meningitis again appeared and on this occasion no response was obtained with intrathecal therapy, three injections of 15,000 units. Autopsy revealed pus containing streptococci in the subtentorial region and an abscess in the internal ear which was discharging through the auditory nerve canal.

Repeated intrathecal injection of 15,000 units on successive days did not kill streptococci in the subtentorial region. Cisternal puncture might have proved more effective. Pus in the internal ear and the petrous temporal bone was beyond reach of penicillin given by any method, and caused repeated meningeal infection.

Case 84 was one of compound, depressed fracture of the skull with severe laceration of the dura and right frontal lobe. Depressed bone was removed, the wound was excised and sutured and a fine tube was left in the depth of the wound. The dura could not be completely closed. A prophylactic course of penicillin was given intramuscularly, 360,000 units in three days, and penicillin solution, 100 units per cubic centimetre, was injected twice a day for six days through the tube into the depths of the wound. The patient was apparently well for the first ten days and his wound had apparently healed; the sutures were removed. A culture of *Bacillus coli* was obtained. Thereafter the patient complained of headache and his forehead became progressively more swollen. On the thirteenth day the wound broke down, and a cerebral fungus extruded. The cerebro-spinal fluid contained numerous pus cells and no response was obtained with repeated intrathecal injections of penicillin. The patient died two days later from cerebro-spinal meningitis. From swabs taken from the brain and meninges at autopsy a pure culture of a coliform bacillus was grown.

Penicillin produced no effect in the presence of an insensitive organism.

Empyema.

Penicillin passes into the pleural cavity, but in the presence of a large effusion becomes diluted. Consequently it is advisable to give it parenterally to deal with any lung infection, and into the empyema cavity after aspiration. By these means the pus can be sterilized rapidly. It has been our experience and that of others[39] that an empyema has to be drained in many cases despite penicillin therapy, but that the patient is rendered less "toxic" and recovery is hastened.

Case 67 was one of massive right-sided pleural effusion containing numerous pus cells and hæmolytic streptococci, inhibited by 0·0078 unit of penicillin per cubic centimetre. The patient was treated for six days by daily aspiration and intrapleural injection of 20,000 units of penicillin. After the second day degenerate forms of streptococci could be seen in the pus, but no growth was obtained with culture. The patient's condition had improved, but he still had considerable fever. Intramuscular injections of 15,000 units of penicillin every three hours were commenced on the sixth day and were continued until 700,000 units had been given. Throughout the patient's condition was excellent, but fever continued and on the sixteenth day the empyema was drained. Progress since then has been satisfactory, but a broncho-pleural fistula has developed.

Joint Infections.

Four patients suffering from infective arthritis of joints, all due to a hæmolytic *Staphylococcus aureus*, were treated. Although

penicillin is excreted into the knee joint, parenteral therapy alone does not appear to be completely satisfactory, and if progress is not rapid in the first few days it is advisable to inject penicillin into the affected joint, if it is easily accessible, for example, the knee joint.

Case 23 was one of septic arthritis of the knee joint following arthrotomy. Penicillin was given intramuscularly in doses of 15,000 units by the "cumulative" routine. Swelling and pain subsided to a small degree, but then remained unchanged for a further sixteen days. At this stage intramuscular therapy was ceased and 5,000 units of refined calcium penicillin were injected into the joint on alternate days. Pain and residual swelling were rapidly relieved.

Case 45 was one in which a circular saw wound opened into the metacarpal joint of the left wrist. After two and a half months the patient presented a stiff, swollen and extremely painful wrist with an unhealed wound from which was grown a hæmolytic *Staphylococcus aureus*, inhibited by 0·03 unit of penicillin per cubic centimetre. After a total dose of 1,600,000 units the wound had healed, all swelling and tenderness had subsided, and three weeks later a tendon graft operation was performed.

Gas Gangrene.

Gas gangrene organisms are sensitive to penicillin, and animal experiments have demonstrated that good results can be obtained when treatment is commenced within six hours of the artificial infection.[30] [31] Gas gangrene does not always become evident in man so early with the result that treatment is delayed beyond the optimum time. It remains to be seen whether prophylactic penicillin treatment will reduce the incidence of this dangerous infection, but three cases have been reported in which gas gangrene developed despite prophylactic treatment, both local and parenteral.[32] [33]

Penicillin acts solely on the bacteria, and has no effect on bacterial toxins. Therefore, the appropriate antitoxin should be administered together with penicillin.

Case 98 was one of extensive and deep laceration of the first interosseous space. Sulphanilamide powder was applied and the wound was sutured. Three days later clinical gas gangrene was present with swelling of the hand, wrist and fingers. *Clostridium welchii*, grown in culture, was inhibited by 0·015 unit of penicillin per cubic centimetre; it was pathogenic to a guinea-pig. The wound was opened, the subcutaneous tissue was grey and œdematous, the interosseous muscles were pink, but would not contract. Two fine rubber tubes were inserted into the wound. Penicillin solution, 10 units per cubic centimetre, was instilled every two hours. Twenty thousand units of sodium penicillin were given intramuscularly every three hours for six days—a total of 720,000 units. By this time the wound was cleaner and almost all swelling had subsided, but *Clostridium welchii* was still recoverable from the wound. The whole hand was enclosed in a modified Bunyan-Stannard bag into which penicillin solution, 100 units per cubic centimetre, was instilled by constant drip. The wound continued to improve, but after five days *Clostridium welchii* was again recovered. Penicillin-sulphanilamide powder, 5,000 units per gramme, was then applied twice daily for three days. The wound was clean and granulating and sterile. A skin graft was applied four days later.

Parenteral and local therapy resulted in rapid resolution of the cellulitis. The solutions used for local application were too weak and the remaining organisms were not killed until the powder was applied. Had solution containing 250 units of penicillin per cubic centimetre been used, the good result would have been obtained earlier.

Eye Infections.

Good results are claimed in eye infections when penicillin is instilled into the conjunctival sac.[19] Three cases of eye infection that we have treated were all severe, and it was felt that local should be combined with parenteral therapy.

Case 66 was one of deep corneal ulcer with extensive œdema and hypopyon. The condition resolved completely in seven days, leaving only a small opacity. Penicillin, 250 units per cubic centimetre, was instilled into the conjunctiva at hourly intervals and a total of 1,400,000 units was given intramuscularly.

Ear Infections.

Two patients suffering from *otitis externa* were treated; in both cases hæmolytic *Staphylococcus aureus* and hæmolytic streptococci were recovered. Penicillin instilled into the auditory canal proved ineffective. In one case intramuscular administration of penicillin for a period of forty-eight hours induced complete resolution and in the other a chronic eczema of the meatus, pinna and side of the face developed during treatment and was unaffected by penicillin. Soon after treatment was discontinued rapid improvement occurred.

Local Therapy.

The importance of direct application to an area of infection cannot be over-estimated. By this means any desired concentration can be obtained and maintained with the use of comparatively small amounts of penicillin.

Local therapy is recommended in the prophylactic treatment of recent wounds and compound fractures, and in the treatment of localized or surface infections, chronic sinuses, abscess cavities, in fact, wherever solutions, powders or ointments can be brought into effective contact with the infecting organism, and may be used alone or in combination with parenteral methods.

Soft Tissue Wounds.

Treatment of wounds with penicillin is no excuse for disregard of surgical principles. Even greater care must now be adopted in preparation of the area and excision of the wound than was the custom in the past. Foreign bodies, debris and dead tissue must be removed because they cannot be "sterilized" by penicillin. Incomplete excision and *débridement* of wounds and their treatment by penicillin and suture may be followed by infection more disastrous in its effects than was experienced when wounds were left open.

Unnecessary sacrifice of skin and fascia should be avoided, so that suture can be performed without undue tension. Undercutting is frequently necessary to relieve tension or to make possible apposition of skin edges when there has been skin loss.

Since penicillin must be allowed access to all parts of a wound, it is advisable to suture the skin only and not to close the wound in layers.

A frequent complication of wounds treated with penicillin is infection by coliform organisms with or without *Bacillus proteus* and *Bacillus pyocyaneus*. These are insensitive bacteria which appear to flourish in the absence of sensitive organisms. Wounds so infected discharge pus which is thin and characteristically salmon pink in colour; if *Bacillus pyocyaneus* is present the pus turns green on the dressing. The pus may be discharged between wound edges or through suture wounds; if dead spaces exist, pus may accumulate there and finally escape by bursting through the suture line. Despite the presence of this type of infection, the wounds remain surprisingly free of inflammation. The presence of "pink" pus is not an indication for interference with the wound because primary healing occurs with little delay. From our experience it is advised that sutures be left *in situ* for twelve to fourteen days, because with earlier removal the wound edges may separate. In four wounds treated by excision and locally applied penicillin, sutures were removed between the eighth and tenth days, when primary union appeared complete. Two to three days later the wound edges in every case were found to have separated over one-third to two-thirds of their length, revealing markedly little healing reaction in the tissues beneath. Opportunity was taken in the following case to obtain sections from two wounds, one penicillin-treated, the other untreated.

Case 85 was one of deep laceration of the leg. The wound was excised, sprayed with penicillin-sulphanilamide powder and sutured, a small tube being placed in the wound. Three cubic centimetres of penicillin solution (250 units per cubic centimetre) were injected into the tube twice daily for four days. At the time of operation a sebaceous cyst of the thigh was excised and the wound was sutured. The sutures were removed on the twelfth day. On the fourteenth day small blocks of tissue were excised from across each wound.

Sections revealed that in the penicillin-treated wound the epithelial growth over the wound area was poor, and that granulation tissue was less in extent and poorer in capillaries and that the fibroblasts were less mature (Figure XVII).

After excision penicillin may be distributed through wounds as a powder or in solution.

Powder. Penicillin-sulphanilamide powder, 2,000 to 5,000 units per gramme, is used. It may be applied to tissue surfaces with a spatula, but the most satisfactory method is insufflation. The amount required varies with the area of the wound, but 0·5 to 4·0 grammes is usually sufficient. One level teaspoonful of powder is equivalent to four grammes, while the Royal Air Force type of powder insufflator delivers one gramme with 50 "puffs".

Hæmostasis is essential to prevent the powder from being washed away while the wound is being sutured. Penicillin is highly diffusible, and when it is used in this way its action is comparatively evanescent; with the wound once closed there will be no further opportunity for local treatment.

Recent wounds which have become infected can be prepared rapidly for secondary suture by application of penicillin powder twice a day.

Solution. "Crude" calcium penicillin is used in strengths of 250 to 500 units per cubic centimetre. Lower concentrations are less effective. Ten, twenty, fifty and one hundred units per cubic centimetre have been tried in a few cases, but proved unsatisfactory.

One or more lengths of four or six gauge rubber tubing are inserted before the wound is sutured, either through the wound itself or through separate stab wounds (Figure XVIII). The

ILLUSTRATIONS TO THE ARTICLE BY DR. R. OFFICER, DR. JOHN LOEWENTHAL AND DR. J. W. PERRY.

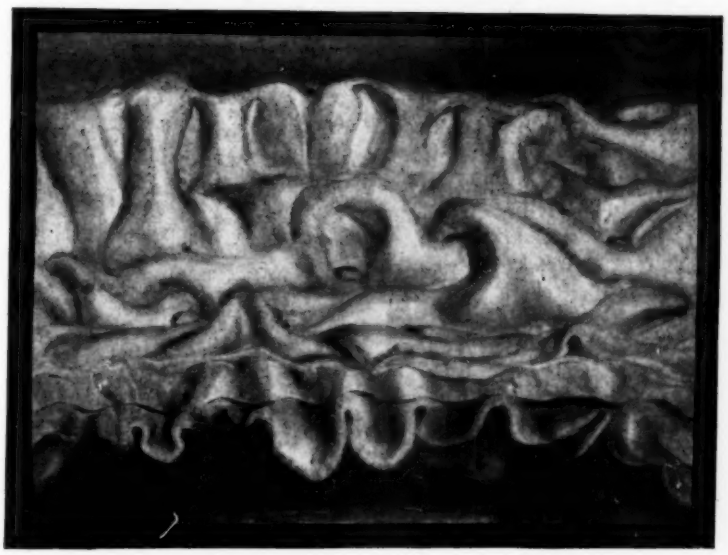

FIGURE I.
Penicillium notatum after eight days' growth.

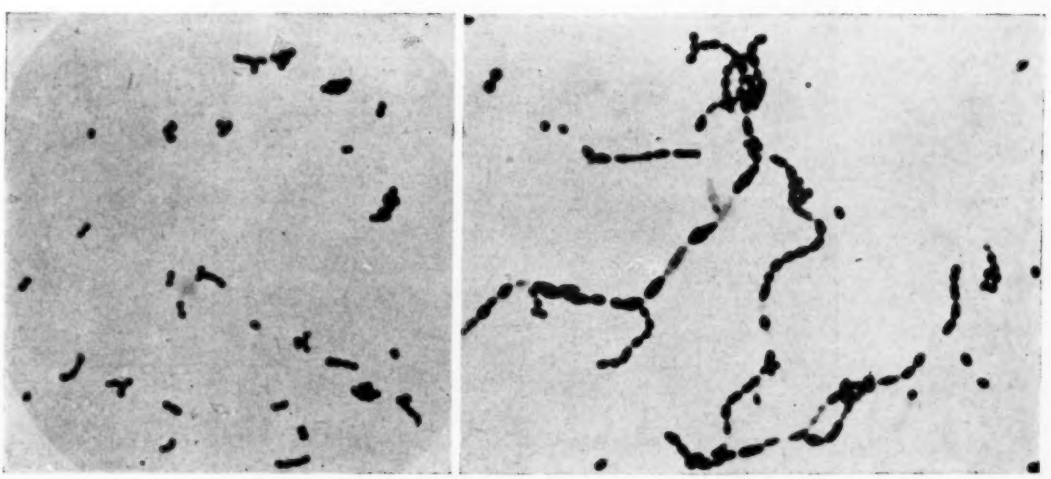

FIGURE II.
Morphological changes produced by growth in a subinhibitory concentration of penicillin. (*a*) Streptococci grown in a patient's serum before penicillin. (× 1,400.) (*b*) Streptococci grown in the same patient's serum one and a half hours after penicillin undetectable, following an intramuscular injection of 20,000 units of penicillin. (× 1,400.)

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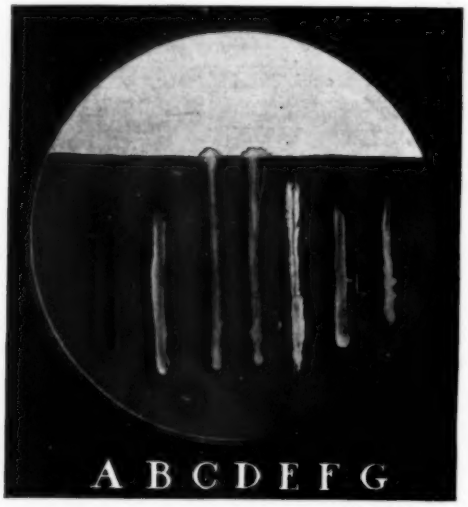

FIGURE III.

Qualitative test for sensitivity of organisms. A = *Hæmolytic streptococcus*; B, E, F, G = sensitive strains of *Staphylococcus aureus*; C = *Bacillus coli*; D = a comparatively insensitive *Staphylococcus aureus*.

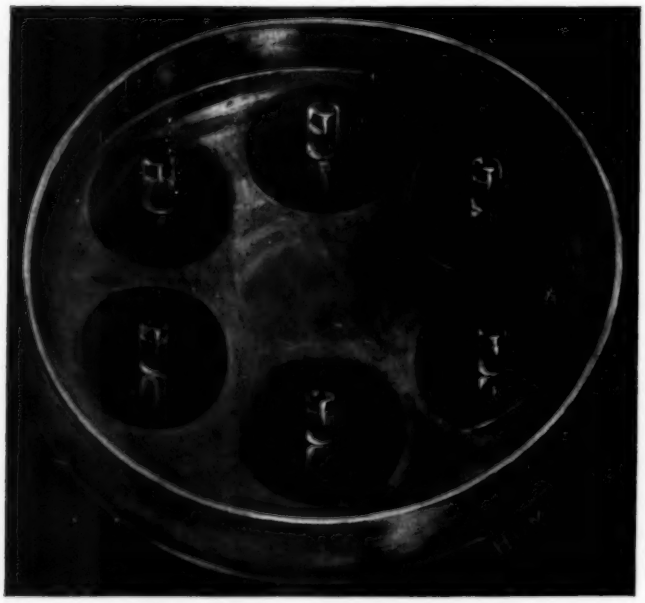

FIGURE IV.

Agar plate showing the Oxford method of penicillin assay.

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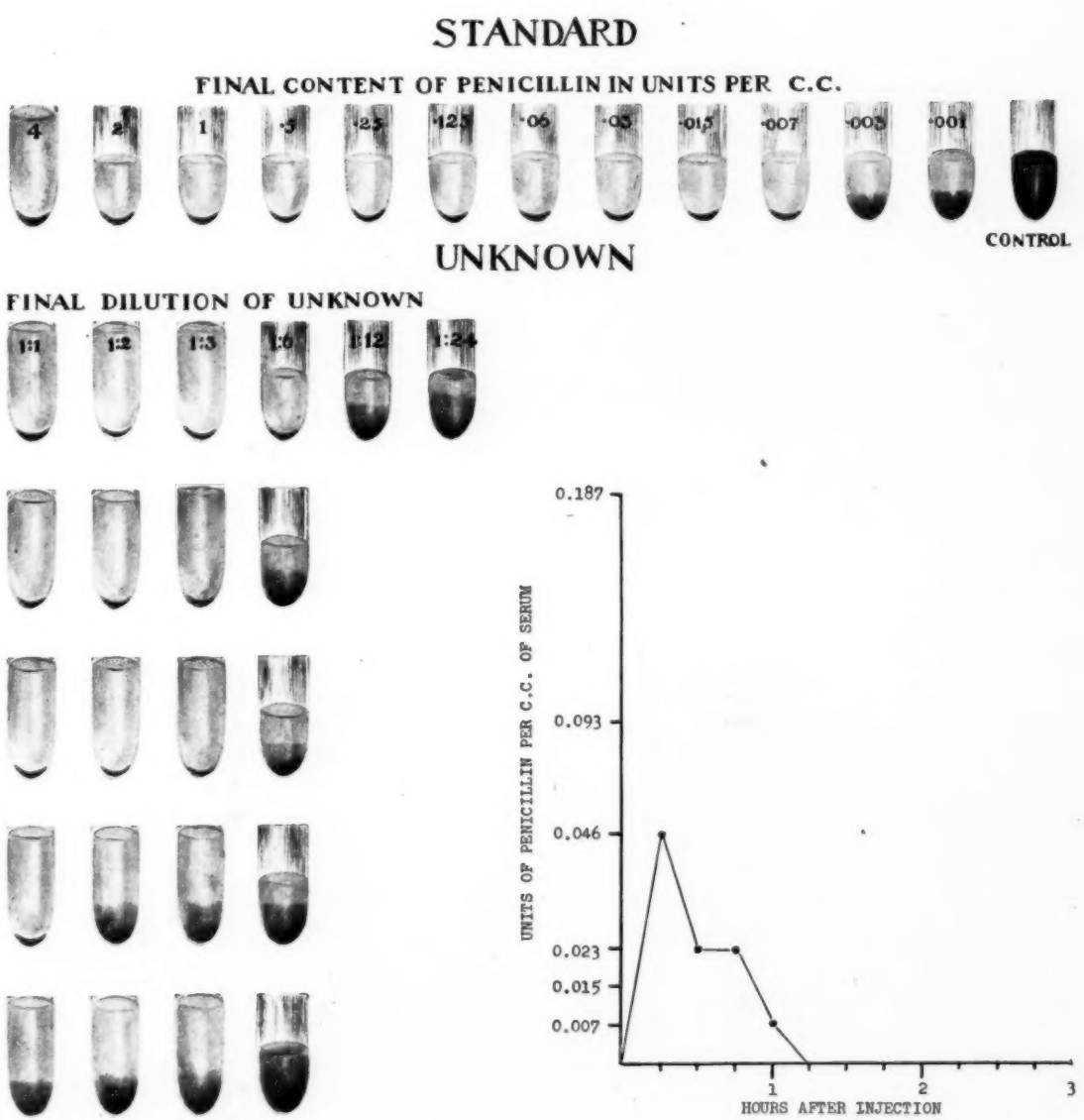

FIGURE V.

Result of serial dilution method of assay of sera collected at fifteen-minute intervals after an intramuscular injection of 10,000 units of penicillin, and graph derived from these tests. (Read in conjunction with Table IV.)

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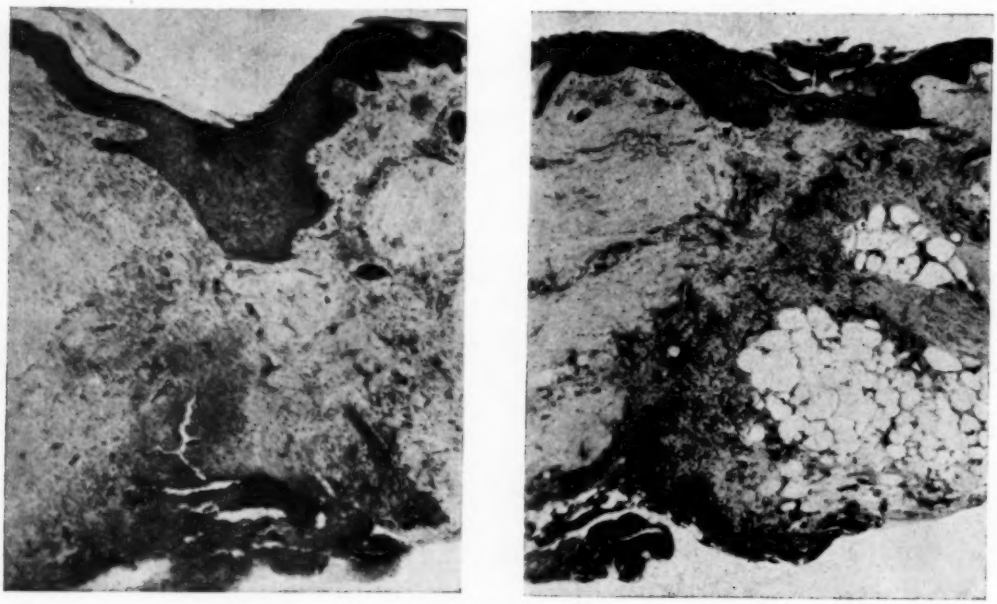

FIGURE XVII.

Photomicrographs of sections taken fourteen days after (*a*) suture of a wound untreated with penicillin (× 40); (*b*) suture of a wound with local penicillin treatment (× 40).

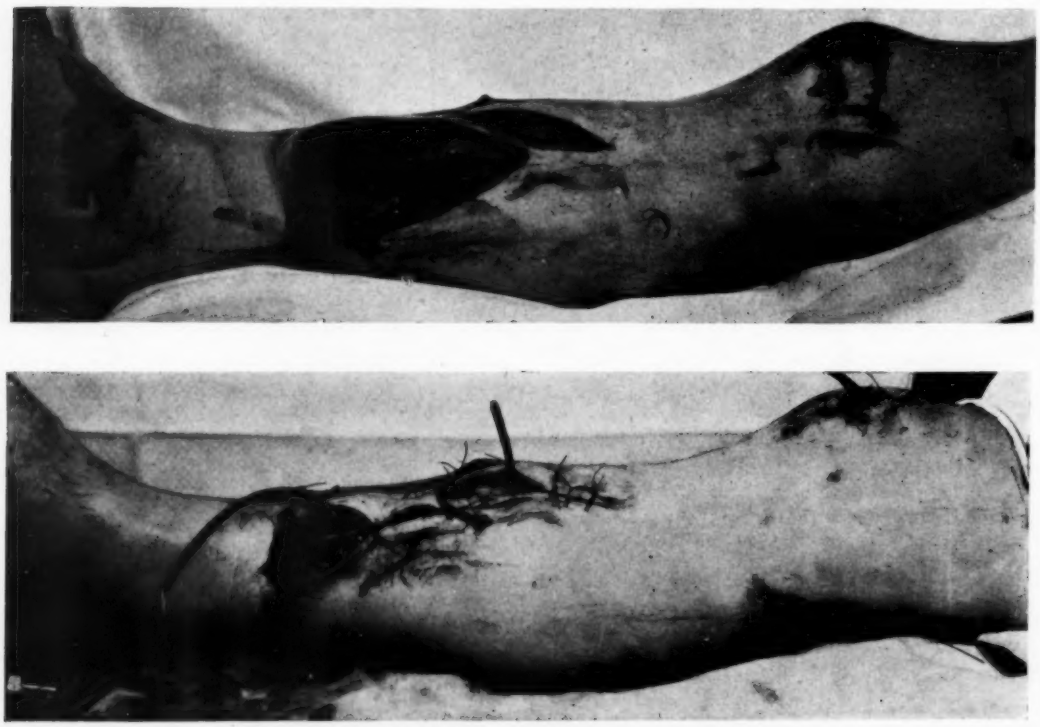

FIGURE XVIII.

Compound fracture of the tibia and fibula illustrating the use of penicillin tubes for local therapy in conjunction with wound suture.

tubes protrude through the dressing, their ends being clamped or plugged with a glass spigot. Three to five cubic centimetres of solution are injected into each tube twice daily with a rigidly aseptic technique. To maintain asepsis a sterile syringe is required for each case. Where large numbers have to be treated, the apparatus illustrated in Figure XIX allows of economy in syringes and rapid injection. It consists of a 100 cubic centimetre bottle with a rubber stopper through which run two tubes, the first being connected to an air filter and the other by small bore pressure tubing to an automatic two-way valve (de Wahl Davis type) and syringe. The outlet of the valve is connected by one piece of pressure tubing to another short length of tubing from which projects a glass nozzle. The glass nozzle is attached to the tubes leading into the wounds and solution is easily and rapidly injected in measured quantities by filling the syringe with the required amount and pushing home the piston. To maintain asepsis, a separate glass nozzle is used for each case, the short length of rubber tubing is boiled at the completion of a round and the whole apparatus is boiled or autoclaved after the use of each 100 cubic centimetres of fluid. To avoid sticking, the valve should be washed through with water before sterilization.

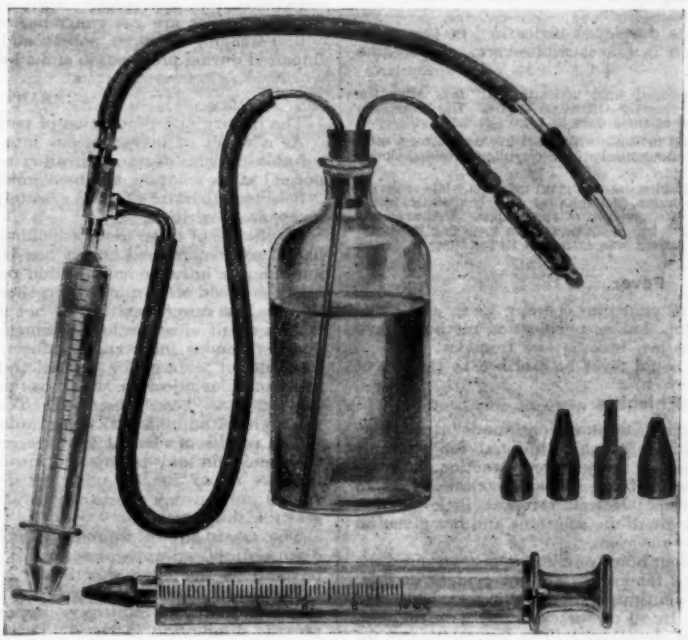

FIGURE XIX.
Apparatus for the injection of penicillin in local therapy into penicillin tubes and chronic sinuses.

Compound Fractures.

Treatment is carried out in the same manner as described for soft tissue wounds. Correct and thorough *débridement* and excision are essential preliminaries to the application of penicillin and suture of the wound.

Extensive tissue damage associated with compound fractures of long bones is an indication for combined parenteral and local administration, owing to difficulty in the distribution of penicillin to all parts of the wound by local instillation alone.

Case 6 was one of compound fracture of tibia and fibula with extensive tissue damage and laceration of knee extending into the joint. Both wounds were excised and sutured, three tubes being placed around the fracture, one into the knee joint and one in the extraarticular tissues (Figure XVIII). The wound of the leg could not be completely sutured on account of skin destruction.

Penicillin solution, 500 units per cubic centimetre, was injected into each tube twice daily for eight days, the tube in the knee joint being removed after the first injection. Intramuscular injections of 15,000 units were given every three hours for five days. The wound of the knee healed by primary union. The wound of the leg healed in eight weeks, partly by primary union and partly by granulation; at no time were there signs of inflammation. Union is proceeding satisfactorily.

Case 93 was one of gun-shot wound of the hand. Entry was in the palm and exit through an extensive cruciate laceration on the dorsum. Fracture of third metacarpal bone was present, with extensive muscle damage. The wound was excised and sutured, with a tube in the region of the fracture. Penicillin solution, three cubic centimetres of 250 units per cubic centimetre, was injected twice a day for two days. The sutures were removed on the fourteenth day. The wounds healed. There was no evidence of infection at any time.

Burns and Granulating Wounds.

Major Rank[35] has treated 25 burns and granulating wounds from which streptococci or staphylococci, or both, were isolated. Penicillin-sulphanilamide and penicillin-serum powder were both used.

His conclusions were:

1. Satisfactory results were obtained when the powder was applied daily, but equal effect, more rapidly produced, resulted from applications twice a day.

2. Marked improvement in the condition of the wounds was seen in two to five days.

3. Hæmolytic streptococci were eliminated in two to three days, while staphylococci disappeared more slowly, daily cultures revealing progressively fewer organisms until after about five days none could be grown. After cessation of treatment organisms often recurred in cultures, staphylococci more readily than streptococci.

4. Though many surface cultures showed no growth after three to five days of treatment, it was common for Gram-negative organisms to appear whether penicillin was continued or not.

5. No local damaging effect was noted on any wound.

Osteomyelitis.

Local therapy has been used in fifteen cases, by injection of penicillin solution into sinuses or by instillation into tubes placed in wounds following sequestrectomy.

In the treatment of chronic sinuses, the solution must penetrate throughout the whole extent of the lesion, considerable pressure being required. Such pressure cannot be attained by insertion of a tube or catheter into the sinus, but the nozzles illustrated in Figure XIX have proved efficient. They are short lengths of fine bore rubber pressure tubing, with conical ends; shaping was done by grinding on a dental emery wheel. With these rubber tips attached either to a "Record" syringe or to the glass nozzle of the apparatus illustrated, solution can be injected under pressure. It has been our experience that the volume of fluid injectable increases during the first two to three days, probably because extensions of the sinus are opened; then as healing occurs, the amount decreases. Injections should be continued twice a day until the sinus is almost healed, usually two to four weeks.

Staphylococci and streptococci, originally isolated from sinuses, disappear rapidly, to be replaced in many cases by coliform organisms. If therapy is ceased too early, staphylococci can again be obtained in culture, but streptococci rarely recur.

Case 5 was one of gun-shot wound through the upper end of the tibia with a fracture extending into the knee joint. Septic arthritis and osteomyelitis subsequently developed, but subsided after parenteral penicillin therapy. Four months later the knee ankylosed and a sinus was present extending to the fracture site. *Staphylococcus aureus* grown in culture was inhibited by 0·06 unit of penicillin per cubic centimetre. The sinus was injected with calcium penicillin solution morning and evening for fifteen days. Culture contained coliform organisms and *Bacillus pyocyaneus*. The sinus healed after a further eighteen days.

Case 42 was one of gun-shot wound of the tibia, with subsequent chronic osteomyelitis. A bone cavity and sinus remained after sequestrectomy at four months. At seven months the wound was excised, the cavity was curetted, and the wound was closed with a penicillin tube placed in the bone cavity. Penicillin solution, 250 units per cubic centimetre, was injected morning and evening for seven days. The wound was infected with *Bacillus coli* but healed in five weeks. No further discharge occurred and an X-ray photograph shows the cavity filling with newly formed bone.

Case 75 was one of gun-shot wound of the left thigh with a compound fracture of the femur. The patient had a stormy post-operative period. Hæmolytic *Staphylococcus aureus* and *Bacillus coli* were cultured from the wound. Five weeks after infliction of the wound the patient was given a course of penicillin, 1,000,000 units, with considerable improvement in his general condition, but staphylococci were still recoverable from the wound. Sixteen weeks after receipt of the wound the patient was still febrile, very thin and "toxic". Hæmolytic streptococci were grown from the wound. Calcium penicillin solution, 250 units per cubic centimetre, was instilled into sinuses

and this resulted in considerable general improvement and only *Bacillus coli* and *Bacillus proteus* were cultured from the wound. Four weeks later two large and six small sequestra were removed, little union being found present between bony fragments. A penicillin tube was inserted and penicillin was instilled for a further fourteen days. Four weeks after sequestrectomy discharge ceased, sinuses healed and clinical union was apparent.

Complications of Penicillin Therapy.

It is a remarkable fact that so few complications are encountered when so large a portion of the material injected consists of impurities.

Urticaria.

Urticaria has been reported in 12% of a series of 209 cases.[23] Its onset may occur during or after a course of treatment, whether local or parenteral.

Three of our 141 patients developed urticaria; in two cases the condition was mild and in one it was severe. Adrenaline gave but temporary relief.

In Case 26 the patient developed mild urticaria four days after the completion of intramuscular therapy—1,200,000 units. The condition subsided gradually over a period of three days.

In Case 50 the patient had mild urticaria with onset five days after a total dose of 800,000 units, given intramuscularly; the condition subsided slowly in five days.

In Case 46 the patient had a sudden onset of giant urticaria while receiving injections of calcium penicillin solution, 250 units per cubic centimetre, into a sinus associated with chronic osteomyelitis of the carpus. Urticaria was followed in twenty-four hours by angio-neurotic œdema involving the head, trunk and all the limbs. The patient was extremely ill for three days and then gradually recovered.

Fever.

During the early days of penicillin therapy fever and chills were comparatively common, but as purification methods have improved, their occurrence has become less frequent.

In no case in our series could fever be ascribed to the use of penicillin.

Phlebitis.

Phlebitis is a frequent complication of continuous intravenous administration of penicillin. Strong solutions, for example 250 units per cubic centimetre, cause severe reaction, whereas phlebitis of less degree results from solutions containing 50 to 100 units per cubic centimetre. Herrell[23] reports little reaction resulting from the use of more dilute solutions and has given an infusion for eight days into one vein.

After sixteen to twenty-four hours swelling appears around the site of injection. Pain and tenderness are not evident at first, but if administration is continued the swelling extends and becomes red and tender. In all of our cases, eight in number, phlebitis of varying degree developed. The longest period for which a single vein was used was sixty-six hours, and severe phlebitis resulted. Later it was made the practice to change the site of injection every twenty-four hours, and no severe reactions occurred.

Headache.

One patient complained of severe frontal headache, commencing ten minutes after each injection of 15,000 units and lasting for approximately two hours. The pain became progressively worse and after three days therapy had to be ceased. Thereafter the patient experienced no further headache.

Abdominal Pain.

One patient experienced mild upper abdominal discomfort of a colicky nature. The pain commenced during a course of therapy by continuous intravenous infusion, and subsided when treatment was completed. During a subsequent course by intramuscular injection the same pain was experienced.

Increased Blood Urea Content.

Florey and Florey[19] reported a rise in the blood urea level in some of the early cases in which they used penicillin for treatment.

Daily blood estimations have been made in five of our cases. In all there was a rise of seven to ten milligrammes *per centum* in the blood urea content during the first five days of treatment. Return to normal occurred three to four days after penicillin therapy was completed. The raised blood urea level was not accompanied by albuminuria.

Increased Blood Calcium Content.

No significant rise in the calcium level has been detected in the blood of patients receiving a daily dose of 100,000 to 200,000 units of "refined" calcium salt by intramuscular injection.

Principles of Treatment.

In conclusion, the following principles are postulated as a guide to treatment with penicillin.

1. The infecting bacteria must be sensitive to the action of penicillin. When possible, organisms should be recovered and tested.
2. The active principle must be brought into contact with the organisms in sufficient concentration. To attain this it may be necessary to use simultaneously more than one method of administration.
3. Abscesses must be drained.
4. Dead tissue, such as sequestra, must be removed.
5. In the presence of infections caused by exotoxin-producing organisms the appropriate antitoxin must be administered. Such infections are gas gangrene, tetanus and diphtheria.
6. Penicillin must be potent and its potency must not be impaired during preparation and administration.

Summary.

The history and production of penicillin have been described.

As a result of investigations into the stability of penicillin, suitable vehicles of administration were found to be "Soluvac" normal saline solution, sulphanilamide powder and an ointment.

Selected laboratory tests for bacterial sensitivity and penicillin assay are described.

By the use of these tests penicillin levels in various body fluids have been determined and it has been found that after intramuscular or intravenous injection penicillin is rapidly absorbed into the blood stream and from there appears in the urine and diffuses into serous cavities but not into the cerebro-spinal fluid.

As a result of serum level estimations intramuscular injection and continuous intravenous infusion are recommended as the methods of choice for administration. A new routine for intramuscular injection, which has proved less disturbing to the patient, has been described. The hazards of continuous intravenous administration are noted.

The results of clinical trial are given and it has been found that penicillin may be injected intramuscularly or intravenously in doses up to 200,000 units per day, and intrathecally up to 15,000 units a day: into serous cavities 20,000 units may be given without risk.

The treatment of wounds with locally applied penicillin is discussed and an apparatus for use when a number of patients have to be treated is described.

Early symptomatic response has been found to be the outstanding feature. Subjective improvement is rapid and may precede diminution in signs. Patients' appetites improve and they sleep for long periods and awake refreshed. In acute cases return to normal occurs in a short period, but in chronic cases the subsidence is slower and the conditions have a tendency to recur.

Complications encountered in the treatment of 141 patients are enumerated.

Used within its limitations, penicillin has proved to be a valuable therapeutic weapon.

Acknowledgements.

We are indebted to the Director-General of Medical Services for permission to publish this paper.

Appreciation is also expressed for the advice of Brigadier W. A. Hailes, Colonel E. V. Keogh and Major P. L. Bazeley.

The work has been performed at an Australian military hospital, and we thank the Commanding Officer, Colonel D. J. Thomas, and his staff for facilities placed at our disposal.

Dr. F. G. Morgan, Director of the Commonwealth Serum Laboratories, and his staff have rendered invaluable assistance.

Our thanks are due to members of the Australian Army Nursing Service and Australian Army Medical Women's Service for their enthusiastic and untiring efforts.

We are grateful to Private L. R. Hume, who was responsible for the colour illustrations.

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Reports of Cases.

A NOTE ON CUTANEOUS LEISHMANIASIS IN THE TERRITORY OF PAPUA.

By A. J. MAY, M.R.A.C.P.,
Lithgow, New South Wales.

DURING the year 1943-1944, three patients suffering from cutaneous leishmaniasis were seen at the native hospital established by "ANGAU" near Port Moresby. In two of the cases the lesions took the form of a granuloma in the inguinal fold; the tumour was elongated and gutter-shaped and the edges were red, thickened and raised, and bled easily. In the other case a facial lesion was present on the left cheek; it consisted of an area about two inches in diameter which was raised, thickened and darkly pigmented.

Scrapings from the edges of the two inguinal lesions and fluid obtained by puncture from the edge of the facial lesion were examined by Mr. Christain. He demonstrated the presence of inclusion bodies of a Leishman-Donovan type. The specimens were subsequently seen by Major A. V. Jackson, pathologist to an Australian general hospital, who confirmed the foregoing findings.

The inguinal lesions were treated as follows. Under anæsthesia they were scraped with a sharp spoon and then painted with pure phenol. A course of antimony injections ("Anthio-maline") was given also, and the lesions cleared up fairly quickly (in about one month). It was not possible to find out whether any relapse occurred later, as many granulomata tend to recur.

The facial condition reacted slowly to a full course of antimony injections. A course of sulphapyridine given later had little effect, and this lesion was remarkable for its chronicity. No "Fouadin" was available—I have found this effective in other types of tropical granuloma—and it was not possible to use an ointment of antimony applied locally.

These cutaneous leishmaniasis lesions are apparently more common among the natives of the territories than was formerly realized.

I would like to thank Lieutenant-Colonel Mack, Major A. V. Jackson and Mr. Christain for their cooperation.

A CASE OF OSTEOMYELITIS OF THE ODONTOID PROCESS OF THE AXIS.

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AND
E. H. DERRICK,
Department of Health and Home Affairs, Brisbane.

FRANK,[1] in reporting a case of osteomyelitis of the odontoid process of the axis, commented on its rarity; this suggests that our case also should be put on record.

Clinical Record.

G.P., a male child, aged one year and ten months, was admitted to the Brisbane Children's Hospital on July 23, 1942. His mother stated that he had been feverish for the past five days, complaining of a sore throat. His breathing had seemed to be difficult at night, but he had no cough.

On examination he had a temperature of 101° F. and was flushed. His tonsils were swollen and red and the pharyngeal wall was inflamed. A number of tender, enlarged, cervical glands was present along both sterno-mastoid muscles and at the angles of the jaw. The child's neck was not stiff, his ear drums were normal, and no other abnormality could be detected elsewhere.

He was given sulphapyridine (0·25 gramme every four hours) and kept at rest in bed, hot foments being applied to his neck. In spite of this treatment his temperature remained elevated, rising to 103° F. each evening. The enlarged cervical glands on the right side increased in size, and after five days the swelling became fluctuant and was opened under general anæsthesia. About half an ounce of thick pus was evacuated and a piece of rubber glove drain was inserted.

Drainage from the incised abscess was free; but although the child's temperature fell somewhat, his general condition did not improve. The administration of sulphapyridine, which had been stopped on July 26, was recommenced on July 31, doses of 0·5 gramme being given every four hours; but again the drug was given without noticeable benefit. A second abscess developed just lateral to the right sterno-clavicular joint, and this was opened without anæsthesia on August 3. A quantity of pus was liberated, culture of which produced a pure growth of *Staphylococcus aureus*.

Meanwhile the child had become flushed, and had developed rapid, grunting breathing and a short cough. Some fine râles had been detected at the base of the right lung. On August 6 clinical signs of right-sided pneumo-

thorax were suddenly manifested; the child was distressed and breathless, his heart was displaced towards the left axilla, the percussion note over the right side of the chest was hyperresonant, and the breath sounds were very faint. On the same day it was noticed, however, that not all the child's respiratory distress could be explained on the basis of the pneumothorax. He was unable to swallow saliva, and showed evidence of obstruction to his airway by inspiratory stridor and recession of the lower end of the sternum and the epigastrium.

No abnormality could be seen on inspection of the throat, but with a finger in the mouth one could discern a large, tense swelling behind the pharyngeal wall on the right side of the mid-line. This was considered to be an acute retropharyngeal abscess.

Preparations were made at once to open the abscess without anæsthesia. The child was laid across the bed and his head was gently hyperextended over the edge. Under good illumination and with a gag in the mouth a knife was plunged into the abscess, pus being liberated; but as this was done the child suddenly became limp in the nurse's arms and appeared dead. No pus seemed to have been inhaled, but on the assumption that some might have been sucked into the air passages, the trachea was opened and found empty. The child was considered already dead when this was done, stimulants and artificial respiration having proved of no avail. The sudden collapse was attributed to vagal inhibition of the heart. The case was reported to the coroner, who ordered an autopsy.

Autopsy Findings.

The body of the child was well nourished. Externally were present a healed scar below the right ear, a nearly healed scar over the sternal end of the right clavicle and a fresh tracheotomy wound.

In the posterior wall of the pharynx was a recent surgical opening leading into a retropharyngeal abscess. Here was a mass of inflamed tissue with thick, reddish pus coming from the region of the body of the second cervical vertebra. The odontoid process was found to be denuded of periosteum and surrounded by pus. Its cap of cartilage had separated from the main bony part of the process. Pus was present in both the horizontal components of the atlanto-axial joint and was spreading down on the posterior surface of the body of the axis. It had not penetrated the dura or caused meningitis. The separation from the odontoid process of its epiphysis and periosteum with their attachments, and the inflammatory softening of neighbouring ligaments, had permitted abnormal mobility of the atlas.

The tonsils were not enlarged or inflamed. No abnormality was detected in the larynx. The trachea was normal, apart from the tracheotomy opening. The right lung was completely deflated and contained an abscess, 0·4 inch in diameter, in the lower lobe just beneath the pleura. The pleura was thickened generally and in the basal part contained a layer of greenish pus and fibrin. There was no free pus in the pleural cavity. The left lung was normal except for a little deflation. Examination of the liver and kidneys revealed slight toxic spoiling. The spleen appeared normal. There was no intracranial abnormality.

Discussion.

Our interpretation of the illness is that it began with tonsillitis followed by a secondary cervical adenitis. At some stage a bacteriæmia developed with metastatic foci in the right lung and in the axis. A pneumothorax followed the lung lesion; the osteomyelitis of the axis led to a retropharyngeal abscess as well as to damage to the odontoid process and a general loosening of the ligaments around. Gentle hyperextension of the head then caused separation of the epiphysis of the odontoid, dislocation of the atlas, compression of the cord and sudden death. The illness lasted altogether nineteen days.

Isolation of the *Staphylococcus aureus* from the second abscess inculpates it as the cause of the illness. The organism is a common inhabitant of the throat and periodically produces infections of the upper part of the respiratory tract. It is frequently isolated in pure culture from the trachea in cases of acute laryngo-tracheo-bronchitis, in which it is probably a secondary invader to a virus infection.

Acknowledgement.

We are indebted to Sir Raphael Cilento, Director-General of Health and Medical Services, Queensland, for permission to publish such of this information as pertains to the Department of Health and Home Affairs.

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Reviews.

FORWARD SURGERY IN WAR.

WHEN the civilian surgeon becomes an army surgeon he learns many new methods and techniques; he also learns that he is one of a team who will treat the patient under his care. W. H. Ogilvie, in "Forward Surgery in Modern War", states that his remarks are addressed "to the general surgeon in one of the services who is already trained in operative technique, but new to the surgery of wounds in modern warfare", and that they are intended "to acquaint him with methods that have proved their value and to warn him of known dangers".[1] From the pen of such a well-known surgeon, and in view of his experiences as consultant surgeon to the East Africa and Middle East Forces, the reader expects the work to be of high standard and general excellence; he will not be disappointed.

The book is essentially practical in its outlook and gives a sound basis upon which the surgeon who first sees the wounded man can form his judgement. One of the main differences between civilian and military surgery is that in civil practice one surgeon usually carries out the whole of the treatment from beginning to end, whereas in the services each surgeon must realize that he is only one of a series of surgeons who will treat the patient. None must appreciate this difference more than the surgeon working in a forward area, who must do for his patient what is safest at the moment. Ogilvie stresses this point continually in this book, and lays down what in his opinion is the safest thing to do in changing circumstances.

Notwithstanding the concise manner in which the various subjects are dealt with, there appear to be no serious omissions. Due importance is given to the use of the various sulphonamides in the prophylaxis of sepsis in wounds, and although mention is made of penicillin, the opinion is expressed that "in forward areas it has no real advantage over the sulphonamides". It will be interesting to read the reports which are to be published in due course following the present battles in Western Europe on the use of penicillin in forward areas. In the treatment of wounds and fractures, while demanding immobilization, Ogilvie issues a timely warning against the use of unpadded plaster splints and skeletal traction in these zones. It is noted that he still favours the use of the Thomas splint for immobilization purposes in injuries of the lower limb.

Mention is made of the injection of the stellate and lumbar sympathetic ganglia as a means of overcoming arterial spasm from its many causes, and the technique is described. It is noted that Ogilvie discourages the simultaneous tying of the vein when it is necessary to ligate an artery. This differs from the advice formerly given on these occasions; but the author's experience was that the tying of the vein did not help to ward off gangrene and occasionally led to an œdematous, heavy, aching leg.

The articles on "Abdominal Wounds" and on "Chest Wounds" contain much good and sound advice, emphasizing the urgency of active treatment in the one and the need for expectant treatment in the other.

When dealing with wounds of the head and face, Ogilvie stresses the need for early evacuation to centres treating these specific casualties; he points out that forward surgery should content itself with life-saving measures only.

This book should be read and studied by all men in the services; it should be of special use to the surgeon who first comes in contact with the wounded man. After reading it, too, every surgeon will realize better the need for the "technical instructions" which are periodically issued and which at the time often cause medical officers to feel that all individuality has gone; but he will again be impressed with the reminder that he is a member of a team. The author obviously knows his subject and is giving the considered opinions resulting from his vast experience.

[1] "Forward Surgery in Modern War", by W. H. Ogilvie, M.A., M.D., M.Ch., F.R.C.S., Hon. F.A.C.S., Hon. F.R.C.S.(C.); 1944. London: Butterworth and Company (Publishers) Limited. 8¼" × 5¼", pp. 99, with illustrations.

The Medical Journal of Australia

SATURDAY, NOVEMBER 4, 1944.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: Initials of author, surname of author, full title of article, name of journal, volume, full date (month, day and year), number of the first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

PENICILLIN.

THE visit of Sir Howard Florey to Australia and the lectures that he gave in the capital cities have been of great value to the medical profession and the people of the Commonwealth. Not only have medical practitioners, whose interest in penicillin was already at a high pitch, been further stimulated, not only have they had the advantage of hearing from one of the discoverers of penicillin the history of its elaboration, an account of what it will do and a warning of what it will not do, but they have learned something of the spirit of those who did the work. Our visitor has written that "the discovery and development of penicillin may be looked on as quite one of the luckiest accidents that has occurred in medicine, for without exception all other mould antibiotics so far examined are poisonous". While it is no doubt true that there was, as Sir Howard Florey told his Australian audiences, an element of luck in the choice of the mould that was investigated by the Oxford workers, all who have heard the story of the investigations, will see them as an orderly sequence of events, and will have some idea of the inspiration that came from the head of the team. Sir Howard Florey spoke in the warmest terms of those who have worked with him, and declared that no head of a laboratory could carry out such an investigation without the very material help of willing collaborators highly skilled in special aspects of the work; we may be quite sure that these workers would say much the same kind of thing about the inspiration of their chief. The public in Australia will in the long run profit from Sir Howard Florey's visit, apart from what they will gain as a result of his influence on practising doctors. The story of penicillin as told in the newspapers captured the popular imagination and people were prepared to listen to what its discoverer had to say. Here was an Australian, they thought, who had gone to England to lose himself in the world of science, and who had appeared again as a world figure, having found a remedy of which wonderful, almost incredible, tales were told. When he spoke of science in Australia and of Australian scientists at work in Australia, he was clearly one who spoke with authority and to whom heed should be paid. That his words may have important results is a subject that cannot be discussed at the moment; we must concern ourselves with penicillin and its use. Unfortunately no contribution by Sir Howard Florey will be published in this journal. When asked for an account of his work that Australian practitioners not privileged to hear him might read in their own journal something that he had written, he felt compelled to decline for two reasons. The first was that he had nothing new to add to what he had published already in other journals; the second was that in any case his itinerary in Australia (he was in the hands of the army authorities and of the Commonwealth Government) was so crowded that he had no time to put pen to paper, much as he would have wished to do so. In these circumstances readers are referred to a survey of the development of penicillin published by Sir Howard Florey in the *British Medical Journal* of August 5, 1944. The ground covered in this survey is much the same as that traversed by the author in his Australian lectures.

An enormous literature has already grown up around penicillin. In January, 1944, the second series of an annotated bibliography was published by Winthrop Chemical Company, of New York, and the number at the end of the series reached a total of 260. Many additions to the list have been made since then, and in the present issue we publish a lengthy account of an investigation and clinical trial of penicillin carried out by three officers of the Australian Army Medical Corps, R. Officer, J. Loewenthal and J. W. Perry. This article should be studied and restudied by Australian practitioners, for it is replete with information on every aspect of the subject. In the use of penicillin it is important to remember that it acts as a bacteriostatic agent and that phagocytosis takes part in the process of ridding the body of infection. Both Florey and Fleming have laid stress on the bacteriostatic action of the drug, and Officer, Loewenthal and Perry point out that weight of evidence suggests that the drug acts by interfering with cell division. In practice penicillin is most effective in acute stages of disease, that is, when cell division is at its height; the advantage of administration in the early stages of an infection is thus clear. Florey states that pure penicillin will stop the growth of some kinds of bacteria at a dilution of one in fifty million or more. The drug must come into contact with the active organism. Thus penicillin will not cause the disappearance of an abscess. It will remove all the inflammation around an abscess, but once administration of penicillin is stopped the inflammation will recur. If the abscess is incised and drained the story is different. It is easy also to understand that in chronic conditions when much fibrous reaction has occurred, penicillin will not produce dramatic results. Most important of all is the realization that by no means all bacteria are sensitive to penicillin. The sensitive organisms are well known and are set out in Officer, Loewenthal and Perry's paper. To give penicillin in the treatment of infections by non-sensitive organisms is a futile procedure and a waste of time and money. The only way to avoid this pitfall is to think always of penicillin therapy in terms of the infecting organism and not of the disease from which the patient is said to be

suffering. In regard to methods of administration, Florey has spoken in favour of continuous intramuscular administration. Officer, Loewenthal and Perry mention reports of abscess formation following the use of this method and describe a method of intramuscular injection used by them, with which the patient's sleep is not disturbed and from which they claim good results have been obtained. Whatever method is used, dosage must be adequate and every care must be taken that nothing is done during preparation or administration of the drug that will impair its potency; these questions are dealt with by Officer and his co-authors.

Certain questions relating to the availability and distribution of penicillin in Australia remain for discussion. Before they are mentioned, however, it is fitting that emphasis should be laid on the fact that American workers have been responsible for the large-scale production of penicillin. To express satisfaction at the British origin of penicillin may be understandable; it may be regarded as "legitimate pride", but it may also be invidious. Any statement should be complete. The *British Medical Journal* of August 5, 1944, describes three "victories" in the penicillin field. The first was Fleming's discovery; the second was the victory of Florey and his colleagues who showed how to obtain penicillin in relatively pure form and who demonstrated its clinical use; the third victory lay with the Americans, who showed how to produce it on a large scale. Among the American workers, Dr. A. N. Richards, chairman of the Committee for Medical Research, has been preeminent. Turning to Australia, we note that the Commonwealth Serum Laboratories have been working at high pressure to produce penicillin for the Australian services and for the civilian population. As a matter of fact the people of Australia have been particularly fortunate in the rapidity with which the drug has been made available for civilian use. At first regulations making its use dependent on the completion of certain formalities were introduced, but, with increased production, these, as announced in a recent issue of this journal, have been relaxed somewhat, to the relief of everyone concerned. Ample supplies are being produced and efforts are being made to improve on methods of production. Readers of this journal may not all be aware that Dr. F. T. Wheatland and Major P. L. Bazeley have recently been sent overseas to study penicillin and its production. In regard to supplies of penicillin, objections have sometimes been raised to the prohibition of importation from overseas, especially from America, presumably because of the idea that unrestricted importation would lead to the removal of all regulations covering supply and use. Inquiry has revealed that the importation of the drug was prohibited because of the policy which restricts overseas spending for reasons of finance and exchange. To this, provided stocks in the Commonwealth are adequate and available, no exception can be taken. Two disabilities remain to be rectified. At present the medical practitioner is held responsible for the cost of the drug. This unfortunate practice was mentioned at the recent meeting of the Federal Council, and it is to be hoped that the representations that are to be made to the Commonwealth Department of Health will be effective. The other disability is the restricted availability of the drug. It should be stocked in accessible centres all over the country. Difficulty has been experienced and delay has been caused by the present conditions. A dash through the night by two young women in a motor-car carrying penicillin in a journey of several hundred miles makes a news item for the daily Press that delights in such happenings, but it is an unnecessary episode in the treatment of a patient, is likely to cause delay in treatment and will increase the cost of the drug. No doubt all these disabilities will disappear in time, but there is no reason why this should not be sooner rather than later.

Current Comment.

THE INVESTIGATION OF DIGESTIVE DISORDERS.

CHRONIC or persistent disorders of the upper alimentary tract have proved a very difficult problem in all the armed forces. Their investigation presents many difficulties. Not only must facilities be considered, and these vary greatly under different service conditions, but the not negligible danger of wholesale routine procedures in their possible effect on morale must be borne in mind. The services are, of course, immediately concerned with a man's capacity to serve and his disposal. But there is also the more deliberate and scientific side of investigation designed to illuminate an obscure page of military medicine. Such an inquiry has been carried out among naval personnel suffering from dyspepsia by a team led by Lieutenant-Commander H. Montgomery, and including Lieutenant L. O. Underdahl, Lieutenant H. R. Butt, Captain W. Walters and Professor R. Schindler. The inclusion of Schindler is sufficient warrant that an authoritative gastroscopic examination and report were made on the 45 patients submitted to special investigation. The method followed was to carry out a radiological examination, and unless any contraindications were present, to perform gastroscopy; chemical studies were also made, but sufficient information was not available in this series to evaluate their significance. In addition a psychiatric study was made of each patient without regard to his particular digestive symptoms or the diagnosis arrived at by other methods. The patients had not all been engaged in active service abroad. Some had been exposed to battle hazards and the lesser but nevertheless real trials of tropical service, fatigue and inappropriate food. Others had been on home service and some actually lived in their own homes, thus representing with considerable accuracy the civil portion of the population suffering from digestive troubles. The symptoms complained of were most diverse, but the frequency of pain localized to a triangle bounded by the umbilicus and the sites of the gall-bladder and the spleen is noteworthy. In 23 cases duodenal ulcer was demonstrated by radiological examination. No gastric ulcers were found in this series either by X-ray examination or by gastroscopy. In six cases ulcer gastritis was also certainly present, and in two others doubtfully present. Thus the frequency of the presence of definitely severe gastritis in conjunction with duodenal ulcer such as has been noted in civilian series was not noted. In the ulcer group the psychiatric interviews revealed no severe psychoneurosis. In six cases mild to moderate neuroses were found, but in general the remaining 17 patients showed no evidence of a psychoneurotic background. In the second group of 22 patients neither gastric nor duodenal ulcer was found. In half of them, however, some variety or grade of gastritis was diagnosed by the gastroscopist. The interesting thing is that this non-ulcer group was most significant from the psychiatric point of view. In 11 cases there was a definite psychoneurosis sufficiently severe to warrant discharge from the service, and in the remaining 11, six patients had undoubted neurotic symptoms. Of all these patients, about one-half of those abnormal from the psychiatric viewpoint also had

[1] *The Journal of the American Medical Association*, July 29, 1944.

demonstrable gastritis. Some interesting case histories are supplied in detail.

This investigation is, of course, simply a carefully carried out survey of patients of two classes with which all experienced medical officers in the services are familiar. These two classes are those who have organic disease of the upper digestive tract, and those who, either with or without some evidence of organic disease, have a well-marked digestive fixation. It will, of course, be realized that because psychoneurotic features were not discovered in the patients suffering from ulcer in this series, it is not implied that psychic stress is not an important factor in the cause and recurrence of peptic ulcers. This is well known, and in the same issue of the journal publishing the work quoted above is a warning from the familiar pen of W. C. Alvarez as to the risk of "flare-ups" of peptic ulcers following special nervous stresses. Alvarez advises that ulcer patients should be instructed to take food and antacids every hour or two following an emotional crisis, especially during the night hours. Even if all physicians are not prepared to follow such a drastic though distinguished lead, it must be admitted that in digestive disease, as in other disease, it is the man who is to be treated, and not that false philosophical abstraction, the malady.

THE CHEMOTHERAPY OF TYPHUS.

PERHAPS the recent personal contact with Sir Howard Florey has emphasized to those who have limited knowledge of the methods of the research worker what arduous and endless work must be devoted to the preparation and testing of substances that show therapeutic promise. Florey has described the temporary setback experienced in the early use of penicillin in the human subject when some toxic signs became manifest, and the immense relief felt when the toxic factors were found to be extraneous and eradicable. All workers on therapeutic testing are not so favoured. Typhus, which has attracted so many good medical minds, has been extensively studied during this war from many aspects, including the therapeutic. C. H. Andrewes, M. Van den Ende, H. King and J. Walker have recently published some of their experimental results with new chemical compounds used on rickettsial infections in animals.[1] Up to date, however, the results with man have been disappointing, for not only has therapeutic benefit not been observed, but toxic effects were found in occasional cases, and for these no cause could be given. Fuller details will be welcomed when they are made available. Three different strains of murine typhus rickettsiæ were used, and these were adapted to mouse lungs with varying difficulty. It is interesting that sulphathiazole was given to the mice in order to combat contaminant infections with pasteurella. The mice were infected intranasally under anæsthesia in a special inoculation box, a device which has reduced considerably the hazards of this most risky type of research. The number of foci of infections found in the lungs gives a quantitative measure of the pathogenicity of the rickettsial suspension employed, and thus the effects of therapy may be assessed.

The substances used were known as V147 (*p*-sulphamidobenzamidine hydrochloride) and V186, a corresponding amidoxine. It is curious that, although evidence of the activity of V147 was definite in countering the rickettsial infections in mice, such activity was found to be specific. There is thus little chance of V147 being one of a numerous family all possessing therapeutic properties. It is not at all active *in vitro*, and it is not affected by *p*-aminobenzoic acid either *in vivo* or *in vitro*. Its action is therefore different from that of the sulphonamides, and further research along these lines might possibly yield important results. Certain antibacterial properties are possessed by V147, but these do not appear to be closely related to its anti-typhus powers.

Such a drug, effective by mouth and by subcutaneous or intraperitoneal injection in mice, seemed most promising, but it is apparently ineffective in guinea-pigs, and equally so in man. This work may, however, prove to be significant, and it is to be hoped that it will open other avenues leading to success. Andrewes and his colleagues have investigated seventy other unrelated compounds, and found them quite ineffective. In establishing that a very slight alteration of the molecular structure of V147 destroyed its peculiarly specific therapeutic power, they also examined and rejected 84 related substances. As Zinsser truly said in his own lightly veiled autobiography, scientific discovery is rarely "made by inspiration—a sort of coup de foudre—from on high". We hope that the last step in this search for a cure for typhus will soon be made, and we must again agree with Zinsser when he points out that "only the initiated know and honour those whose patient integrity and devotion to exact observation have made the last step possible".

[1] *The Lancet*, June, 1944.

UNRESOLVED PNEUMONIA.

STUDY of living pathology in cases of pneumonia from which patients are tardy in making a full anatomical recovery, has modified considerably the older conventional teaching of pathology. Non-resolution of pneumonia has so frequently been found to be due to a preexisting bronchiectatic lesion proved by bronchoscopy and bronchography, that the slowly clearing lung promptly arouses suspicion. But there are other factors which have recently brought that characteristic combination found with scientific advances, greater enlightenment and added difficulties. These factors are the large numbers of strong young adults under close scrutiny in the services, and the greater prevalence and freer recognition of atypical pneumonia. The signs of atypical pneumonia may occasionally take months in disappearing from the lungs, and this on the one hand may cause undue suspicion of a more serious lesion such as tuberculosis, or on the other hand may lead us to forget the possibility of bronchiectasis. G. S. Grier has found in studying forty military patients with unresolved pneumonia that two-thirds of them had originally been diagnosed as suffering from atypical pneumonia, whereas in reality the condition was pneumonitis superimposed on bronchiectasis.[1] He recognizes that the initial diagnosis is often difficult. The history may be helpful, especially if the patient complains of recurrent cough or hæmoptysis, but such a story is not always forthcoming. As Grier points out, it is an arresting fact that forty patients with bronchiectasis were admitted to a station hospital in fifteen months, an additional proof, if any be required, of the opinion of physicians that only tuberculosis surpasses bronchiectasis as a cause of chronic pulmonary disease. A routine X-ray examination may fail to reveal bronchiectatic lesions, and this was well demonstrated in some of Grier's patients. The technique followed for the bronchographic studies was to introduce the iodized poppy-seed oil by a laryngeal cannula after preliminary sedation and cocainization of the throat. The flow of the oil was directed by appropriate posturing of the patient, checked by fluoroscopic examination. Postural drainage was employed after the patient returned to the ward. Two cases of some interest are mentioned in which the diagnosis of atypical pneumonia was confirmed, and in these atelectasis was clearly demonstrated by the bronchogram, but six weeks later this condition was proved to be reversible, and complete recovery showed that there was no permanent lesion.

Grier concludes that bronchographic studies should be made in all cases of pneumonia which fail to resolve within four or six weeks. This is rather an extreme recommendation, but this work is a reminder of the well-known propensity of bronchiectasis to be associated with recurrent attacks of pneumonitis. It also points a moral, that in enthusiasm for what may be called "new" diagnoses, we should not forget teachings which are still true and apposite.

[1] *Archives of Internal Medicine*, June, 1944.

Abstracts from Medical Literature.

MEDICINE.

Hodgkin's Disease.

H. JACKSON, JUNIOR, AND F. PARKER, JUNIOR (*The New England Journal of Medicine*, January 6, 1944), in the first of a series of articles state that they divide Hodgkin's disease into three types, paragranuloma, granuloma and sarcoma. They consider that it is essential to recognize the existence of these three forms of the disease, for the pathological picture, the clinical aspects and the prognosis differ materially with each. The "Reed-Sternberg" cells are present in each type, and one type may be transformed into another with the passage of time, but a reverse transformation never takes place, that is, a Hodgkin's sarcoma does not revert to a granuloma. The authors discuss fully the historical data available and the ætiology of the disease, with special reference to the infectious and neoplastic theories. The disease may occur at any age from birth to throughout the first seven decades of life; is commonest in young adults and affects males more often than females, especially in children. The tuberculin test has been employed by various investigators in an attempt to prove or disprove a direct relation between Hodgkin's disease and tuberculosis. Cases of Hodgkin's granuloma have almost uniformly been anergic, reacting, if at all, only to low dilutions—1 in 10 or 1 in 100, rarely 1 in 1,000. The result of the test often becomes positive, frequently strongly positive, after effective X-ray therapy. In the authors' own series of 237 cases, the authors found coexistent active tuberculosis in 20%.

Meningococcal Infections.

W. G. BERNHARD AND A. C. JORDAN (*The Journal of Laboratory and Clinical Medicine*, March, 1944) have discussed the diagnosis of meningococcal infections from smears and cultures of the purpuric lesions. A special culture medium was used. This consists of 14 grammes of bacto dextrose proteose number 3 agar, 15·3 grammes of bacto nutrient agar, 3·2 grammes of soluble starch, dissolved in 1,000 cubic centimetres of water and autoclaved. The medium is brought to a temperature of 90° C. and 5% of rabbit or human blood is added. The medium is dispensed in six-inch tubes and slant. Large amounts of spinal fluid are inoculated to obtain the best results. An extreme variation in the size of the meningococci was noted. Forty patients had purpuric skin lesions tested. The purpuric area having been cleansed with alcohol, a 20-gauge needle was inserted almost parallel with the skin surface into the centre of the petechial spot, care being taken not to go deeply enough to draw peripheral blood. By gentle squeezing several drops of blood and serum were extravasated, and culture tubes were inoculated and smears made of this material. A Gram stain was made at once, and numerous Gram-negative intracellular diplococci were demonstrated. At eighteen hours a typical colony growth appeared on the culture medium. In 27 out of 40 cases a typical organism was demonstrated on smears within thirty minutes.

Pseudobronchiectasis following Atypical Pneumonia.

B. BLADES AND D. J. DUGAN (*The Journal of Thoracic Surgery*, February, 1944) have found that "atypical pneumonia" is capable of producing temporary dilatations of the bronchi in the affected parts of the lungs. The symptoms and bronchographic appearances are those of true bronchiectasis; but after four to six weeks further bronchography shows that restitution to normal has occurred or is in progress. The authors call the condition pseudobronchiectasis. A point of differentiation from true bronchiectasis is that the sputum does not separate into three layers on standing.

Diabetes Mellitus.

ELLIOTT P. JOSLIN (*The New England Journal of Medicine*, April 6, 1944) has discussed progress in *diabetes mellitus*. Diabetes can be produced in three ways, by removal of the pancreas, by repeated injections of anterior pituitary extracts, and finally by injection of alloxan, the ureide of mesoxalic acid. This substance is closely related to the purines. Injection intravenously of 100 to 300 milligrammes of alloxan per kilogram of body weight, in a 2% solution of distilled water, causes extensive necrosis of the islands of Langerhans of the pancreas. Hyperglycæmia occurs, the blood sugar content rising to 380 milligrammes from 100, 50 or even 30 milligrammes. During the low blood sugar phase, convulsions frequently occur. A 50% solution of glucose given intravenously when convulsions occur keeps the animals alive, and they are found to develop true *diabetes mellitus*. Such selective necrosis of the islands of Langerhans has rarely been described in human beings. The disease in these laboratory animals closely approaches the human disease. A dual onset of diabetes is produced when rabbits are given 40 milligrammes of alloxan per kilogram in repeated intravenous injections.

Respiratory Infections.

C. B. FAVOUR (*The New England Journal of Medicine*, May 4, 1944) reports an epidemic of respiratory infections in the Peter Bent Brigham Hospital under the title "Infections Associated with an Epidemic of Primary Interstitial Pneumonia". The terms pneumonitis, primary interstitial pneumonia and atypical pneumonia all appear to be used to describe the same condition. In the series reported one of the doctors developed cough and fever up to 104° F. Next day X-ray examination revealed extensive pneumonia. The patient remained at work for five days and then went to bed with severe symptoms of a respiratory infection, cough, cyanosis, delirium and bilateral pulmonary mottling similar to that seen in terminal miliary tuberculosis. He was ill for three months. Seventeen days after exposure four contacts of this patient developed cough with fever, and two of these nurses had gastro-intestinal upsets. Three other nurse contacts developed severe tracheo-bronchitis and gastro-enteritis with prostration. No enteric pathogens were isolated. After two weeks' lull in respiratory infections in the hospital another patient was admitted with severe atypical pneumonia. Of ten direct contacts of this patient seven became ill in from one to fourteen days, two with colds, three with tracheo-bronchitis and two with pneumonia. In spite of strict isolation technique with masks and gowns and scrubbing, five of twelve contacts developed tracheo-bronchitis, one pneumonia, one cold and three gastro-intestinal upsets. The incubation period varied between nine and thirteen days. From one of these patients with atypical pneumonia six contacts became ill with tracheo-bronchitis, pneumonia and gastro-intestinal upset. Among all those affected, student nurses suffered much more frequently than graduate nurses, house officers or visiting doctors who had been repeatedly exposed to atypical pneumonia during previous years. Cross infections in the hospital became too numerous to follow, and it was decided to take the temperature of all persons working with patients at 4 p.m. daily. This brought under notice all those with fever and most of those with symptoms. For two months more than 16 to 30 members of the staff were in bed daily on account of infection with what was called virus infection. During nine months 231 out of 300 hospital personnel who had direct contact with patients suffered from epidemically related infections, that is, atypical pneumonia, tracheo-bronchitis, a fatigue syndrome and fever of unknown origin. Twenty-nine persons developed atypical pneumonia. In these cases X-ray examination revealed varying pictures of consolidation or mottling. The patients with pneumonia were those who had been most directly in contact with other patients with pneumonia or those most overworked. Patients with tracheo-bronchitis tended to relapse on reexposure to virus infections, and many had several relapses. Fatigue syndrome was associated with fever below 100° F., and fever lasting for one to three days occurred in 21 cases. No pathological data are given. The diagnosis of atypical pneumonia is said to have been based on X-ray examination, failure to respond to sulphonamides, negative bacteriological studies and eventual recovery.

Thiouracil in the Treatment of Thyreotoxicosis.

E. M. WATSON AND L. D. WILCOX (*The Canadian Medical Association Journal*, July, 1944) discuss the use of thiouracil in the treatment of thyreotoxicosis. They review the literature from the experimental background and the therapeutic application of the drug, and report on the treatment of eleven patients with the drug. In nine of the eleven thyreotoxic patients treated, definite clinical and metabolic improvement occurred following the exhibition of the drug. The symptoms were relieved, the basal metabolic rate was reduced to normal or near normal levels, the pulse was slowed, the body weight was increased, the blood cholesterol content was increased, and a reduction in the amount of circulating thyreoid hormone as indicated by a return to the normal concentration of the organic iodine of the blood was

noted. No toxic effects were observed, periodical blood count examinations failed to reveal the development of anæmia or leucopenia, and there was no suggestion of the development of toxic hepatitis. The authors are of opinion that there does not seem to be a tendency toward the development of a state of refractoriness with respect to this drug *per se*, as is known to occur in the case of persistent iodine therapy. The response to thiouracil by patients previously treated with iodine was slower. The authors admit that the permanency of the improvement and the end results of this type of chemotherapy await decision. The mode of action of thiouracil in depressing the functional activity of the thyreoid gland is largely conjectural at the present time. The situation is a paradoxical one, inasmuch as the provocation of thyreoid hyperplasia with diminished iodine content of the gland is accompanied by a decrease of the hormonal secretion. The thyreoid hyperplasia is presumably a secondary phenomenon described as a "hyperplasia of frustration", occurring in response to the induced relative hypothyreoidism. A disquieting feature, noted clinically, is the failure of the drug, in most instances, to reduce the size of the goitres. Prolonged experience with the use of the drug will decide its true value as a therapeutic agent, its limitations, and its ultimate practical utility.

The Nutritional Role of Cholesterol in Human Coronary Arteriosclerosis.

CARL F. CHAFFER (*Annals of Internal Medicine*, June, 1944) reviews the nutritional role of cholesterol in the genesis of human atherosclerosis based upon a study of one hundred patients in the age period of forty-five to sixty-five years. These patients suffered from peptic ulcer and had received treatment for at least five years, the majority for ten to fifteen years, and some for thirty-five years. The treatment, in the main, had consisted of the use of milk and cream and antacids, and no patient was selected in the series who had not relied upon the use of milk and cream for the relief of discomfort. It was considered that a history of prolonged intermittent therapeutic use of milk implied an abnormal increase in cholesterol in the diet, and met the requirement of a nutritional factor. Clinical evidence of coronary artery occlusion was considered to be coronary artery occlusion with myocardial infarction, *angina pectoris* and certain conduction disturbances of the heart associated with arteriosclerosis. Five hundred patients were used as a control in the study, and these were in the same age period, with the same sex ratio, and none of them had received peptic ulcer treatment or had any manifest endocrine disorder. It was found that the incidence of coronary arteriosclerosis in the studied group was no greater than in the control group. The author refers to the observations made in laboratory animals that have indicated hypercholesterolæmia of nutritional origin to be a factor in the development of atherosclerosis. He states that the relation of hypercholesterolæmia, especially when associated with lipæmia, to the increased incidence of atheromatosis in inherited and acquired endocrine disorders in man is definite, but that the evidence presented from this investigation gives doubtful significance to the nutritional role of cholesterol in the genesis of human atherosclerosis, unless there is an associated disorder of the endocrines.

Electrocardiographic Studies in Old Age.

LEO M. TARAN AND MILTON KAYE (*Annals of Internal Medicine*, June, 1944) present a study of electrocardiographic findings of one hundred and two men and women, sixty to ninety years of age, who had no history or symptoms of cardiovascular disturbances. The findings are arranged in three age groups, 60 to 69, 70 to 79, and 80 to 90 years of age. Three-quarters of the group had left axis deviation, and only 2% showed a right axis deviation. Conduction disturbances were found in 17·6% of the cases, and abnormal conduction was noted more frequently in the older age group. In nearly one-half of the cases evidence of myocardial damage was present. This evidence was found more commonly in the eighth decade than in any of the others, and less commonly in the ninth decade. Abnormal deviation of the initial deflection and the *T* wave and abnormalities in the *Q R S* complex were found more commonly as age advanced. Deviation of the *S-T* segment was found only in the eighth decade.

The Mobilization of Iron in Hæmochromatosis with Administration of Various Chemicals.

HAMILTON R. FISHBACK (*The Journal of Laboratory and Clinical Medicine*, July, 1944) has studied the effect of the administration of various chemicals to a man with hæmochromatosis, given over a period of seven days each, with the purpose of attempting to mobilize stored iron. The intake of iron was kept to a known low level, and the output of urinary and fæcal iron was determined. The results do not indicate any striking effect on iron balance by the chemicals given, namely, sodium thiosulphate, ammonium chloride and sodium bicarbonate. Sodium thiosulphate in large daily dosage caused a low negative iron balance, but this was outweighed greatly by the iron loss of the control period due to escape of blood in the stool.

Coronary Disease Associated with a Short P-R Interval and a Prolonged A R S Complex.

S. A. LEADER (*The Journal of Laboratory and Clinical Medicine*, July, 1944) discusses coronary disease associated with a short *P-R* interval and a prolonged *A R S* complex in the electrocardiogram. He briefly reviews the controversial literature written around the mechanism of this interesting manifestation of a short *P-R* interval and a prolonged *A R S* complex, and states that apart from all theories and conjectures it is definitely known that: (i) it occurs in the absence of organic heart disease; (ii) it occurs most often in young people who are subject to paroxysmal tachycardia (auricular); (iii) occasionally paroxysmal fibrillation occurs in place of the tachycardia and very rarely ventricular tachycardia instead of auricular tachycardia; (iv) it has been produced experimentally in animals by setting up an abnormal conduction pathway between the auricles and ventricles; (v) it has been abolished by the use of atropine, quinidine and exercise, and it may return to normal rhythm spontaneously; (vi) it occurs much more often in males than in females. The author refers to the contribution of Wood, Wolferth and Geckler, who made serial sections of the heart from a patient whose electrocardiogram had shown a short *P-R* interval and a prolonged *A R S* complex, and who had died during an attack of paroxysmal tachycardia. Histological studies revealed three muscular connexions at the right lateral border of the heart between the right ventricle and the right auricle, two of which bridged a small part of the ventricular cavity during their course. It was concluded that this furnishes adequate support for the hypothesis of an accessory auriculoventricular conducting pathway to explain this electrocardiographic anomaly. The author presents the clinical notes of a patient, illustrated by electrocardiograms, in whom the original tracing showed a short *P-R* interval and a prolonged *A R S* complex. This same rhythm was maintained, even though the patient subsequently developed definite evidence of severe coronary disease, except for a transitory return to a normal pattern during an attack of severe precordial pain.

T Wave Inversion in Neuro-circulatory Asthenia.

WEBSTER MERRITT (*Annals of Internal Medicine*, May, 1944) discusses inversion of the *T* waves of the electrocardiogram in two patients with neurocirculatory asthenia. He refers to the fact that until a few years ago, inversion of the *T* waves in Lead I or Lead II of the electrocardiogram was considered as evidence of organic heart disease, and that recently, however, certain exceptions to this general rule have been reported. The author draws attention to various reports in recent literature illustrating the influence of body position, diaphragmatic level, respiration, drugs, tobacco smoke, and over-ventilation, upon such *T* waves in patients who have normal hearts. The case histories and electrocardiograms of two patients suffering from neuro-circulatory asthenia are presented. The electrocardiograms showed temporary, slight inversion of the *T* waves in the second lead, but in all other respects the patients were found to be normal. These electrocardiograms were taken with the patients in the recumbent position, and all factors which occasionally produce *T* wave inversion, such as aforementioned, were eliminated. The author states that the causal factor of such *T* wave inversion is unknown, and likewise the frequency with which it is encountered in the absence of heart disease is not known and will not be determined until large numbers of healthy people have been examined. These phenomena occur in young people, but greater vigilance may reveal that the same phenomena may occur in older people. The discovery of an occasional patient whose whole life has been affected by a mistaken diagnosis of heart disease should remind the physician that it is important to correlate clinical and electrocardiographic studies.

Public Health.

GONORRHŒA IN WOMEN TREATED BY PENICILLIN.

THE following report on the treatment by penicillin of sixty-one women suffering from gonorrhœa has been made by Dr. Beatrice Warner, of the Department of Health and Home Affairs, Queensland, to Sir Raphael Cilento, Director-General of the Department, who has consented to its publication.

Sixty-one women suffering from gonorrhœa received penicillin during ten weeks—April 19 to June 27, 1944. Smears were taken from the cervix, urethra, Bartholin's glands and rectum, and cultures from the cervix, urethra and rectum in all cases immediately before treatment. The cultural method of McLeod and others[1] was used; no culture was reported as "positive, *Neisseria gonorrhœæ* present", unless glucose only of the four sugars, glucose, lactose, saccharose and maltose, was fermented on sub-culture. In all cases except one, culture from one or more of the three orifices was "positive" immediately before treatment. In this exception, Case V (M.W.), smears gave negative results and cultures were overgrown, though on the patient's admission to hospital cultures yielded *Neisseria gonorrhœæ*, and in the ten days preceding her penicillin treatment, smears from the urethra showed Gram-negative intracellular diplococci on two occasions. I consider she was still infected at the time of treatment; penicillin was given before the results of her cultures were known.

In all cases except nine, the expiry date of the penicillin used had been passed. Evidence for comparison of results is insufficient.

Penicillin was administered intramuscularly throughout. In three cases this was supplemented by rectal administration.

These sixty-one patients are considered in two series: (i) those treated at the Venereal Isolation Hospital; (ii) those treated as out-patients at the Women's Clinic.

First Series.

In the first series of 52 patients treated at the Venereal Isolation Hospital, 48 were in-patients; four came from His Majesty's prison. In four cases the infection was acute; in 48 it was chronic—sometimes extremely so. Thirteen patients had received sulphonamides, five of these receiving much local treatment before being given penicillin.

Table I shows the first dosage of penicillin given to 52 patients.

TABLE I.
Dosage of Penicillin.

Number of Patients.	Total Amount of Penicillin.	Amount Given at Each Injection.	Interval in Hours Between Injections.	Remarks.
1	80,000	20,000	3	Absconded before treatment completed.
33	100,000	20,000	3	
1	100,000	20,000	3	100,000 units *per rectum*.
2	100,000	10,000	1	
4	100,000	25,000	2	
1	160,000	20,000	3	
8	200,000	20,000	3	
1	280,000	20,000	3	
1	380,000	20,000	3	

Thirty-eight patients have been discharged or are awaiting discharge from hospital after the first course of penicillin, the standard of discharge from hospital being at least six "negative" smears and attempts at culture, five of which must be made at weekly intervals.

Six, seven, eight or nine negative results have followed attempts to obtain cultures over periods of observation from five and a half to twelve weeks. Two patients have been discharged, having received penicillin followed after an interval by "M & B 760" (31 grammes). These cases appear as recurrences after penicillin in Table II.

The following case shows some of our pre-penicillin difficulties, and the results of treatment with penicillin.

CASE III.—The patient was admitted to hospital on September 6, 1943. In cervical smears Gram-negative diplococci were present. During her stay in hospital—over nine months—she contracted vaginal thrush, and, though this was not proved microscopically, a *Trichomonas vaginalis* infection of the vagina. These yielded to appropriate treatment. For gonorrhœa, until January, 1944, she received "M & B 693", douches, vaginal tampons, irrigations to a suspected urethra. Three cervical smears and one rectal smear showed Gram-negative intracellular diplococci. On January 6, 1944, diathermy was given to the cervix and urethra at the Brisbane General Hospital. On February 10 culture from the urethra yielded *Neisseria gonorrhœæ*. On March 16, in cervical and urethral smears, Gram-negative intracellular diplococci were present. On March 19 treatment with "M & B 760" was begun (a total of 31 grammes was given). On April 20, in cervical smears Gram-negative intracellular diplococci were present, and *Neisseria gonorrhœæ* was present in a cervical culture. On April 27, at 11.15 a.m., treatment with penicillin was begun; a total of 380,000 units was given, 20,000 units being administered every three hours. On April 28, at 10 a.m., smears were "negative"; in cervical and rectal cultures *Neisseria gonorrhœæ* was present. On April 29, at 10 a.m., in a cervical smear extracellular Gram-negative diplococci were present. Treatment ceased at 5.15 p.m.

In the following six weeks from this patient nine "negative" smears were obtained and negative results followed nine attempts to obtain cultures, the last attempt being made after a vaccine. She has since reported at the clinic, where two smears and attempts to obtain cultures at intervals of a fortnight have given negative results. I regard this patient as cured. In my opinion, only just enough penicillin was given.

In twelve cases gonorrhœa has recurred after the first course of penicillin treatment.

Two cases are complete failures; these are their details.

CASE I.—The patient was admitted to hospital on February 9, 1944, with acute gonorrhœa. In cervical, urethral and rectal smears Gram-negative intracellular diplococci were found. Cervical and urethral cultures yielded *Neisseria gonorrhœæ*. She received 31 grammes of "M & B 760". On March 6, in a rectal smear, Gram-negative intracellular diplococci were present. Culture from the rectum yielded *Neisseria gonorrhœæ*. Rectal irrigations were given, and the rectum was dried and swabbed with "Mercurochrome" for three weeks. On April 8 Gram-negative intracellular diplococci were present in a rectal smear. Rectal irrigations with "Zephiran" (0·5 drachm to one pint), followed by the insertion of cod liver oil plugs into the rectum, were given for ten days. On April 19 Gram-negative intracellular diplococci were present in a rectal smear. Culture from the rectum yielded *Neisseria gonorrhœæ*.

Treatment with penicillin was begun, a total of 280,000 units being given (20,000 units every three hours). Subsequently seven smears and attempts at culture gave negative results, though pus was present in the rectum eight days after treatment. On May 2 (thirteen days after treatment) Gram-negative intracellular diplococci were present in a rectal smear. Culture from the rectum yielded *Neisseria gonorrhœæ*. Irrigations with "Zephiran" were resumed for one week. On May 13 penicillin treatment was recommenced, 100,000 units being given (10,000 units per hour). On May 15 pus was present in the rectum; in a rectal smear Gram-negative intracellular diplococci were present, and culture from the rectum yielded *Neisseria gonorrhœæ*. On May 22 further penicillin therapy was begun, 400,000 units being given (20,000 units every two hours). At the same time cotton-wool swabs soaked in penicillin (250 units per cubic centimetre) were inserted into the rectum three times a day for five days (50,000 units), and after a lapse of three days penicillin (1,000 units per cubic centimetre) was used in the same way (100,000 units). On June 9 pus was present in the rectum. In a rectal smear Gram-negative intracellular diplococci were seen; culture from the rectum yielded *Neisseria gonorrhœæ*. On June 16 "M & B 760" therapy was begun, 31 grammes being given. On June 30 pus in large quantities was present in the rectum; in a rectal smear Gram-negative intracellular diplococci were found; culture from the rectum yielded *Neisseria gonorrhœæ*.

By this time this patient had received 780,000 units of penicillin intramuscularly and 150,000 units by the rectum.

TABLE II.
Recurrence of Gonorrhœa after First Course of Penicillin Treatment.
(Venereal Isolation Hospital.)

Case Number.	Before Treatment.		Units of Penicillin.	Dosage. (Intramuscular.)	Days Before Culture Obtained.	Culture Obtained After Treatment.	Further Treatment.	Remarks.
	Smears: Gram-negative Intracellular Diplococci Present.	Cultures Obtained.						
I	R[1]	R	280,000	20,000 three-hourly.	13	R	Penicillin, ++ *et cetera.*	Failure; see text.
II	R	R	200,000	20,000 three-hourly.	13	R	Penicillin, ++ *et cetera.*	Failure; see text.
IV	—	R	200,000	20,000 three-hourly.	55	R	Penicillin, 100,000 units; 10,000 every hour.	Absconded; possible re-infection. Observation.
VI	C, U[1]	C, U, R	100,000	20,000 three-hourly.	39	R	"M & B 760", 31 grammes.	Since discharged.
XV	—	C, U	100,000	25,000 two-hourly.	3	U	"M & B 760", 31 grammes.	H.M.P.[1] Two "negative" smears; not examined since June 8, 1944.
XVI	—	U	100,000	25,000 two-hourly.	38	C, R	Penicillin, 100,000 units; 10,000 every hour.	Pregnant; observation.
XXIII	—	C, U	100,000	20,000 three-hourly.	39	R	Penicillin, 100,000 units; 10,000 every hour.	Observation.
LII	U	C, U	100,000	20,000 three-hourly.	10	U	Penicillin, 100,000 units; 10,000 every hour.	Observation.
LVII	U	C, U, R	100,000	20,000 three-hourly.	12	R	Penicillin, 100,000 units; 10,000 every hour.	Absconded.
LX	U	C, U	100,000	20,000 three-hourly.	23	R	Penicillin, 100,000 units; 10,000 every hour.	Observation.
XXX	—	C	160,000	20,000 three-hourly.	17	C	"M & B 760", 31 grammes.	Since discharged.
XLIX	U, B, R[1]	C, U, R	100,000	20,000 three-hourly.	28	R	—	Delivered in Brisbane Women's Hospital.

[1] R = rectum; C = cervix; U = urethra; B = Bartholin's glands; H.M.P. = His Majesty's Prison.

TABLE III.
Recurrence of Gonorrhœa after First Course of Penicillin Treatment.
(Women's Clinic.)

Case Number.	Before Treatment.		Units of Penicillin.	Dosage. (Intramuscular.)	Days Before Culture Obtained.	Culture Obtained After Treatment.	Further Treatment.	Remarks.
	Smears: Gram-negative Intracellular Diplococci.	Cultures Obtained.						
XXVII	U, R[1]	C, U, R[1]	200,000	20,000 units every hour.	2	C, U, R	200,000 units; 20,000 every hour.	Six negative cultures in 6½ weeks. Conforms to standard of discharge, Venereal Isolation Hospital.

[1] U = urethra; R = rectum; C = cervix.

It was decided to try to find out how this particular gonococcus would behave towards penicillin in culture. Following the method of Fleming,[2] penicillin was incorporated in McLeod's culture medium in a strength of one unit per cubic centimetre. The plate was inoculated with a pure culture of the gonococcus grown from the rectum. There was no growth.

On July 23 the administration of 1,000,000 units of penicillin was begun, 20,000 units being given every hour. Since then pus has been present in the rectum. "M & B 760" (31 grammes) has been given. On August 4, 1944, Gram-negative intracellular diplococci were present in a rectal smear; *Neisseria gonorrhœæ* was grown on culture.

CASE II.—The patient was pregnant. This case is an almost exact parallel of Case I, except that, in addition to her other treatment, this patient received sulphaguanidine (124 grammes) entirely without benefit before being given penicillin. She received 700,000 units intramuscularly, 150,000 units *per rectum*, and then "M & B 760". On June 26, 1944, in a rectal smear, Gram-negative intracellular diplococci were present; culture from the rectum yielded *Neisseria gonorrhœæ*.

The patient came into labour before being given 1,000,000 units of penicillin, and is at present in the Women's Hospital.

Second Series.

In the second series—those treated as out-patients at the Women's Clinic—nine patients received penicillin. In three cases the disease was acute; in six, chronic. Four patients had received sulphonamides, one receiving much local treatment before being given penicillin. These patients received 200,000 units (20,000 units every hour). Six patients, conforming to the standard accepted at the Venereal Isolation Hospital, may, I think, be regarded as cured after their first course of penicillin treatment.

Gonorrhœa recurred in one case (Table III), which, after a second similar course, also conforms to this standard of cure.

This patient may be regarded as the seventh cured.

Comment.

In the combined series of 61 patients, a total of 47 patients have conformed to this standard of cure, eleven patients are under observation or treatment, two have absconded and have not been found, and one is still in prison and has not been followed up.

In the small number of 58 patients who have been followed up, 44 (or 75·86%) have been cured according to our standard after one course of penicillin. If the one patient

receiving two courses of penicillin and the two patients receiving one course of penicillin and "M & B 760" are included, the cures—again according to our standard—are 31·04%.

Nineteen of the patients in hospital were professional prostitutes. Providing nothing except the usual extensive local preparation before examination is being done by them to vitiate results of smears and cultural examinations, these figures are a great improvement on results obtained with any other form of treatment in women. The apparent cures with "M & B 760"—the standard of discharge from hospital then being five "negative" smears and two failures to obtain cultures—were 50%.

Many cases of gonorrhœa in women must be watched most carefully over a long period before conclusions may be drawn. The results of treatment by penicillin in this small incomplete series—and even in the failures the immediate results must be actually seen to be believed—are not sufficient for any claims to be based on them.

Penicillin is said to be effective in the treatment of syphilis. It has been suggested that penicillin given when gonorrhœa and syphilis occur at the same time may mask or delay the onset of clinical signs of syphilis.

> CASE LIX.—The patient was admitted to hospital on June 22, 1944, suffering from chronic gonorrhœa. Culture from the rectum yielded *Neisseria gonorrhœæ*. The Wassermann test failed to produce a reaction, and the Kline test produced a "doubtful" reaction (+2). The gonococcal complement deviation test yielded negative results. The patient received 100,000 units of penicillin. On July 24 enlarged glands were present in the left groin. The Wassermann test produced a "doubtful" reaction (+++) and the Kline test produced a positive reaction (++++). On August 1 the Wassermann test produced a positive reaction (++++) and the Kline test also produced a positive reaction (++++). On August 7 three small primary sores were seen for the first time; dark-ground examination of serum from these revealed *Treponema pallidum*.

That 100,000 units of penicillin effected an apparent cure in 31 cases must be admitted; but it appears that the initial dosage of penicillin should be increased when and if penicillin becomes available in quantity, if penicillin is to be used alone. Two patients (Cases I and II) responded amazingly to their first dosage; had they been given 1,000,000 or even 500,000 units at first instead of so much in instalments, their results might have been different. The patient, Case VI, suffering from acute gonorrhœa was given 100,000 units of penicillin; had she received an adequate dosage, the immense improvement shown for the first twelve days, before clinical signs of gonococcal proctitis reappeared, might have been permanent.

It appears that, to be safe, the period of observation after treatment with penicillin should still be three months. In Case IV the infection recurred fifty-five days after treatment, though reinfection in this case cannot be excluded. In Cases VI, XVI and XXIII recurrence was proved after thirty-nine, thirty-eight and thirty-nine days respectively. The upper limit of the time taken for gonorrhœa in women to recur after treatment with penicillin is not yet known, and careful observations should be made.

The systemic route appears to be the route of choice in the treatment of gonorrhœa with penicillin.

Our technique of rectal administration leaves much to be desired, but this method proved ineffective in two cases and wasteful in one. Three cases is a small number from which to draw conclusions, but the view that this method is useless is held by others. Abraham, Chain and others[3] state that rectal administration was tried in one subject, but that very little active substance was recovered in the urine, and it was afterwards found that fæces inactivate penicillin, probably by bacterial action. Chain and Florey[4] state that bacteria present in the rectum inactivate penicillin. Garrod,[5] discussing the local treatment with penicillin of mixed infections, including sensitive and resistant bacteria, states that "combined infection by a pyogenic coccus and a penicillinase-producing bacillus may be quite unaffected. In one such case, the lesion being a cavity in which solution could be well retained, hæmolytic streptococci persisted in undiminished numbers. That the reason for this was the destruction of penicillin by the coliform bacillus in the wound fluid, was proved repeatedly by demonstrating that, on withdrawal of fluid after twenty-four hours, its penicillin content was nil".

Rectal gonorrhœa is far more common than is generally supposed, and in women it is very difficult to treat. Hayes[6] reviews the literature and quotes cases complicated by stricture (none has occurred in my experience) in which a colostomy opening was made and the bowel irrigated from above, or even a resection of the rectum was performed.

Infection of the rectum is usually autogenous in women, and without symptoms. Pus is generally present in the rectum. In 703 consecutive cases of gonorrhœa from the Women's Clinic, from 472 (67·14%) at some time rectal smears containing Gram-negative intracellular diplococci were obtained. The diagnosis was made by smears only, so is open to criticism, though from results obtained since cultural examination of material from the rectum has been made as a routine measure, the percentage is underestimated rather than over-estimated. These rectal infections, sometimes so chronic, often so difficult to cure, very often unsuspected, provide a great pool of infection.

In Tables II and III it will be seen that, when one cultural examination only was made, eight infections recurred in the rectum, two infections recurred in the rectum and elsewhere, and three infections recurred elsewhere.

In two of the eight infections recurring in the rectum, a culture was obtained for the first time after treatment with penicillin.

If I may again draw conclusions from a very small number of cases, penicillin followed by sulphonamides seems to be of value. Two patients (Cases VI and XXX, Table II) received "M & B 760" on recurrence of the infection after treatment with penicillin, though the time elapsing between this treatment and "M & B 760" was in Case VI forty-three days. One patient (Case XV) received "M & B 760" promptly, and then gave two "negative" smears; but unfortunately she has not been examined since. On the other hand, in Cases I and II, "M & B 760" following penicillin was of no benefit whatever.

Conclusions.

I would make the following suggestions, when penicillin is available in quantity:

1. That the treatment of gonorrhœa in women should be as follows: (*a*) 200,000 to 400,000 units of penicillin by the systemic route, provided no gross infection of the rectum is present; (*b*) 1,000,000 units of penicillin by the systemic route if a gross infection of the rectum is present.
2. That combinations of penicillin and sulphonamides, either together or closely following each other, should be investigated.
3. That the period of observation of gonorrhœa in women treated with penicillin should be three months.

References.

(1) J. W. McLeod, J. C. Coates, F. C. Happold, D. P. Priestley and B. Wheatley: "Cultivation of the Gonococcus as a Method of Diagnosis in Gonorrhœa with Special Reference to the Oxydase Reaction and to the Value of Air Reinforced in its Carbon Dioxide Content", *The Journal of Pathology and Bacteriology*, Volume XXXIX, Number 1, July, 1934, page 231.
(2) A. Fleming: "Penicillin for Selective Cultures and for Demonstrating Bacterial Inhibitions", *Medical Bulletin*, Volume II, Number 1, 1944, page 8.
(3) E. P. Abraham, E. Chain, C. M. Fletcher, H. W. Florey, A. D. Gardner, N. G. Heatley and M. A. Jennings: "Further Observations on Penicillin", *The Lancet*, Volume II, 1941, page 177.
(4) E. Chain and H. W. Florey: "The Discovery of the Chemotherapeutic Properties of Penicillin", *Medical Bulletin*, Volume II, Number 1, 1944, page 6.
(5) L. P. Garrod: "The Laboratory Control of Penicillin Treatment", *British Medical Journal*, Volume I, 1944, page 528.
(6) H. T. Hayes: "Gonorrhœa of Anus and Rectum", *The Journal of the American Medical Association*, Volume XCIII, 1929, page 1878.

British Medical Association News.

SCIENTIFIC.

A MEETING of the Queensland Branch of the British Medical Association was held on July 7, 1944, at the Mater Misericordiæ Public Hospital, South Brisbane. The meeting took the form of a series of clinical demonstrations by members of the staffs of the Mater Misericordiæ Public Hospital and the Mater Misericordiæ Children's Hospital.

Sulphæmoglobinæmia.

DR. L. B. ELWELL showed a female patient, aged forty-eight years, who had sought medical advice on account of

puffing of the face below the eyes, slight swelling of the hands and feet, and recurrent attacks of deep cyanosis described as "going black". Three years previously she had been successfully treated for moderate hypertension by reduction of overweight. She had suffered from severe headaches since the age of twenty-six years. The patient had been in the habit of taking "A.P.C." powders for the headaches; since they had become more severe and frequent during the past three years she had taken the powders with increasing frequency, but never more than three per day. About two years prior to the meeting she had noticed that her face was becoming puffy below the eyes, especially in the mornings, and some degree of blue colour was noticed in the skin. On medical advice she took half a teaspoonful of mixed salts per day for eighteen months, but the puffiness persisted in the face and was also slightly present in the feet and hands. Then blue-black or inky spots began to appear on the palms, the backs of the hands and the sides of the tongue. For the last six months the whole of the tongue had remained permanently blue. The patient's face used to turn a blue-black colour when she stooped, and she had been having increasingly frequent attacks of what she described as "going black"—brief periods of more intense blueness of the hands and feet with a tendency to "tightness" in the breathing. Between the attacks her "wind" was very fair.

On examination, the patient's skin was seen to be generally slightly cyanotic, and the colour of the whole tongue was striking; it was fittingly described as "mauve-lavendar". Otherwise no particular abnormality was apparent. A trace only of albumin was found in the urine. Blood examination revealed moderate anæmia; the erythrocytes numbered 4,000,000 and the leucocytes 5,700 per cubic millimetre, the hæmoglobin value was 76%, and the colour index was 0·9; 68% of the leucocytes were neutrophile cells and 32% were lymphocytes; slight hypochromia was present and a few microcytes were seen. Spectroscopic examination revealed no abnormality in the platelets. Sulphæmoglobin was present in the blood.

Three days later the patient again presented herself, "with the spots out". Inky-blue spots, almost a centimetre in diameter and of irregular outline, were present on the dorsal and palmar surfaces of both hands; they were not elevated or tender.

Dr. Elwell said that Whitby and Britton had suggested as the most acceptable explanation of the disease the existence of a foreign substance in the blood which favoured a combination of hæmoglobin and sulphur with the reduction of hæmoglobin to methæmoglobin. Acute poisoning by sulphuretted hydrogen did not cause sulphæmoglobinæmia. This fact strongly suggested that some intermediary substance was necessary to enable easy combination to take place between corpuscular hæmoglobin and sulphuretted hydrogen absorbed from the intestine of a constipated subject. In the case under discussion no constipation was permitted, as the patient took salts regularly; but the salts mixture almost certainly included sulphates, which might conceivably expedite the interaction. As a point in the differential diagnosis, Whitby and Britton stated that the cyanosis of methæmoglobinæmia usually disappeared within forty-eight hours after ingestion of the drug had ceased, whilst the leaden tint of sulphæmoglobinæmia persisted for weeks. In the present case the colour had scarcely altered in three days after absorption from the "A.P.C." powders, and the cyanosis was still present a week later. A large number of coal-tar derivatives as well as some other chemicals might produce either sulphæmoglobinæmia or methæmoglobinæmia, or both; the list included phenacetin, acetanilide, "Sulphonal", "Plasmoquine", ammonium citrate, potassium chlorate and drugs of the sulphonamide group.

Myelocytic Leuchæmia.

Dr. Elwell next showed a female patient, aged forty-four years, who had been admitted to hospital on May 3, complaining of pain in the left side of the abdomen, the back and the legs of three months' duration. She had lost half a stone in weight in four or five months. Increasing shortness of breath on exertion and general lassitude had been noticed. The patient had a slight productive cough with blood-stained sputum. She also had a blood-stained discharge *per vaginam*. Her only previous illness had occurred in 1936, when she underwent an operation for cholecystectomy.

Examination revealed the patient to be a sallow-faced woman with an enxious expression. No rash or œdema was evident, and no abnormality was detected in the chest. There was no obvious enlargement of the lymph glands or liver, but the spleen was grossly enlarged and extended well below the level of the umbilicus. No abnormality was detected in the urine. The only other abnormal finding was a large retinal hæmorrhage in the right fundus. A blood count revealed that the erythrocytes numbered 4,380,000 and the leucocytes 80,000 per cubic millimetre, the hæmoglobin value was 63% and the colour index was 0·9. Neutrophile, basophile and eosinophile myelocytes were present. A number of megaloblasts and normoblasts were seen, punctate basophilia was present in a few cells and the platelets were normal.

Dr. Elwell said that the diagnosis was chronic myelocytic leuchæmia. The patient was shown to emphasize the value of extensive arsenical therapy, either with or without deep X-ray therapy, in the symptomatic relief of this disease, which was virtually inevitably fatal. Forkner and Scott, in 1931, had reintroduced arsenical therapy, which had been described as both the newest and the oldest treatment for myelocytic leuchæmia; it dated back to 1878, but had been largely forgotten since the advent of radiation therapy in 1902. Its success depended on the drug's being "pushed" until the leucocyte count was reduced to 10,000 per cubic millimetre, or until toxic effects forced reduction or temporary withdrawal. The dose was gradually reduced again to a maintenance level governed by the leucocyte count, the aim being to keep it at about 10,000 per cubic millimetre or a "high normal". Forkner and Scott held that no patient suffering from chronic myelogenous (or myelocytic) leuchæmia in the early stages failed to be strikingly benefited by arsenical treatment. The best results were obtained by what they termed the rapid and relentless administration of the drug. The maintenance dose had been given for as long as a year without ill-effect. Shorter courses of arsenic and radiation therapy might be used alternately. Dr. Elwell said that in the present case, as a result of arsenical treatment, the leucocyte count was in three weeks reduced to 64,000 per cubic millimetre, the size of the spleen diminished and commensurate symptomatic improvement was noted. As pain in the spleen again became troublesome later, total irradiation was given on three occasions; small doses were used, and the treatment was given at intervals of five and seven days. At the time of the second radiation treatment the leucocyte count had dropped to 15,000 per cubic millimetre, with only a slight increase in the erythrocyte count and the hæmoglobin value. Eight days later the leucocyte count was 8,900 per cubic millimetre; the erythrocyte count and the hæmoglobin value were unaltered. The patient was at this time receiving arsenical treatment, and from then a gradual reduction in dosage to the minimum maintenance dose was effected. On July 4 a blood count gave the following information: the leucocytes numbered 8,900 per cubic millimetre; the erythrocyte count had improved and the hæmoglobin value had risen to 76%. The patient's condition was symptomatically much improved.

(To be continued.)

NOTICE.

THE General Secretary of the Federal Council of the British Medical Association in Australia has announced that the following medical practitioner has been released from full-time duty with His Majesty's Forces and has resumed civil practice as from the date mentioned:

Dr. B. Blomfield, "Craignish", 185, Macquarie Street, Sydney (October 23, 1944).

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 206, of October 19, 1944.

CITIZEN NAVAL FORCES OF THE COMMONWEALTH.

Royal Australian Naval Reserve.

Appointments. — Surgeon Commander Leonard John Dunstone (Retired List) is reappointed to the Active List, while performing the duties of District Naval Medical Officer, South Australia, as from 10th April, 1943, under the provisions of National Security (Naval Forces) Regulations; Max Kimberley Anderson and Richard Robsart Rogers are appointed Surgeon Lieutenants, dated 31st August, 1944, and 4th September, 1944, respectively.

Appointments.—Stephen Percy Baker and John Joseph Herlihy are appointed Surgeon Lieutenants, dated 20th July, 1944, and 21st July, 1944, respectively; Alfred Robert Carter, Lloyd McIlwraith Crawford and Kelvin Sandford Hutchinson are appointed Surgeon Lieutenants (D), dated 2nd September, 1944.

ROYAL AUSTRALIAN AIR FORCE.

Permanent Air Force: Medical Branch.

Temporary Squadron Leader S. W. Lush (1193) is promoted to the temporary rank of Wing Commander with effect from 1st July, 1944.

Citizen Air Force: Medical Branch.

The following Temporary Squadron Leaders are granted the acting rank of Wing Commander whilst occupying Wing Commander posts with effect from 1st August, 1944: G. G. Burniston (261263), J. K. Gabriel (252085).

Temporary Flight Lieutenant F. J. Kenny (254851) is granted the acting rank of Squadron Leader whilst occupying a Squadron Leader post with effect from 1st August, 1944.

The grant of the acting rank of Wing Commander to Squadron Leader G. M. Oxer (251201) is terminated upon his ceasing to occupy a Wing Commander post with effect from 23rd June, 1944.

The following Temporary Wing Commanders are promoted to the temporary rank of Group Captain with effect from 1st July, 1944: (Acting Group Captain) R. B. Davis (251167), (Acting Group Captain) A. H. Baldwin (264907).

The following Temporary Squadron Leaders are promoted to the temporary rank of Wing Commander with effect from 1st July, 1944: (Acting Wing Commander) V. E. Knight (251197), (Acting Wing Commander) C. P. Ley (261213), C. P. Hudson (261240), (Acting Wing Commander) R. W. D. Fisher (251203), R. G. Plummer (281253), (Acting Wing Commander) D. C. Howie (261264), B. J. Basil-Jones (261289), (Acting Wing Commander) G. J. Baldwin (251657), (Acting Wing Commander) F. R. Wicks (281655).

The following Flight Lieutenants are promoted to the temporary rank of Squadron Leader with effect from 1st July, 1944: W. H. Fraser (261656), R. J. Riddell (251660), R. Lloyd-Jones (261773), J. Deane-Butcher (272117), F. T. Humphery (261369), (Acting Squadron Leader) F. J. B. Drake (252835), R. C. Willis (253219), V. J. Odlum (283222), J. S. Boxall (263226), (Acting Squadron Leader) W. T. H. Scales (263240), (Acting Squadron Leader) S. D. Watsford (253263), J. R. McCoy (253345), (Acting Squadron Leader) M. Rohan (253344), (Acting Squadron Leader) D. J. Dowling (253441), J. N. Sevier (263442), W. H. Smith (253443), W. G. Jasper (263897), H. C. Taylor (264368), M. T. Drummond (264589), (Acting Squadron Leader) J. R. F. England (283727), J. W. L. Atkinson (251414), D. Scanlan (267221), (Acting Squadron Leader) J. F. Ziegler (257480), (Acting Squadron Leader) F. J. McCoy (253474).

Reserve: Medical Branch.

The following officers are transferred from the Active List with effect from the dates indicated: (Squadron Leaders) C. A. McHardy (261539), 30th August, 1944, R. E. Ashbarry (253724), 3rd September, 1944.—(Ex. Min. No. 263—Approved 18th October, 1944.)

CASUALTIES.

ACCORDING to the casualty list received on October 24, 1944, Major R. H. Formby, A.A.M.C., College Park, South Australia, has been placed on the "dangerously ill" list.

According to the casualty list received on October 28, 1944, Captain E. McL. J. Baker, A.A.M.C., Sale, Victoria, has been removed from the "seriously ill" list.

According to the casualty list received on October 28, 1944, Colonel H. H. Jamieson, A.A.M.C., North Sydney, has been placed on the "seriously ill" list.

National Emergency Measures.

SUPPLIES OF RICE.

THE following letter from the Secretary of the Department of Commerce and Agriculture (Marketing Division) is published at the request of the General Secretary of the Federal Council of the British Medical Association in Australia.

[COPY.]

COMMONWEALTH OF AUSTRALIA.

Department of Commerce and Agriculture (Marketing Division).

Fourth Floor,
A.M.P. Chambers,
419, Collins Street,
Melbourne, C.1.

Dear Sir,

In order to safeguard supplies of rice for the needs of the fighting services and Pacific islands, it will be remembered that, in conformity with a decision of the Australian Food Council, distribution of this commodity to civilians was suspended. Provision was, however, made for issues of rice to be made in cases of medical necessity upon production of a medical certificate, and this system still operates.

Informal discussions recently took place with a representative of the Victorian Branch of your Association, and the opinion was expressed as to the necessity for whole rice in cases of illness.

Accordingly the matter was referred to the Director-General of Health (Dr. J. H. L. Cumpston) for advice.

A reply has now been received which states that at the last meeting of the Food Rationing (Special Diets) Committee of the National Health and Medical Research Council, attention was given to this matter, and it was agreed that whole rice is not an essential item of diet for any form of sickness to which the white race is subject.

I should be glad if you would be good enough to arrange for this decision to be brought to the notice of members of your Association. It is proposed to continue the issue of permits to obtain rice upon production of a medical certificate up to and including 31st October, 1944, by which time all your members should be aware of the decision.

It might be added that there is no restriction on the sale of ground rice, which is a by-product from the milling process.

Yours faithfully,

(Signed) J. F. MURPHY,
Secretary.

Dr. J. G. Hunter,
General Secretary,
British Medical Association,
135, Macquarie Street,
Sydney, N.S.W.

Australian Medical Board Proceedings.

NEW SOUTH WALES.

The undermentioned have been registered, pursuant to the provisions of the *Medical Practitioners Act*, 1938-1939, of New South Wales, as duly qualified medical practitioners:

Croese, Kelvin Xavier, M.B., B.S., 1944 (Univ. Sydney), Newcastle Hospital, Newcastle.

Dickson, John Grant, M.B., B.S., 1944 (Univ. Sydney), Newcastle Hospital, Newcastle.

Doubleday, Leonard Charles, M.B., B.S., 1944 (Univ. Sydney), Royal Hobart Hospital, Hobart, Tasmania.

Droulers, John-Paul Maurice, M.B., B.S., 1944 (Univ. Sydney), Launceston General Hospital, Launceston, Tasmania.

Dunlop, Barbara Buzzard, M.B., B.S., 1944 (Univ. Sydney), Royal Hobart Hospital, Hobart, Tasmania.

Dunlop, Roger John Massie, M.B., B.S., 1944 (Univ. Sydney), Sydney Hospital, Sydney.

Early, Victor Maynard, M.B., B.S., 1944 (Univ. Sydney), Royal South Sydney Hospital, Zetland.

Egan, Maxwell Christmas, M.B., B.S., 1944 (Univ. Sydney), Royal South Sydney Hospital, Zetland.

Ellis, James Morrison, M.B., B.S., 1944 (Univ. Sydney), Royal North Shore Hospital, St. Leonards.

Falk, Keith Louis, M.B., B.S., 1944 (Univ. Sydney), Saint Vincent's Hospital, Darlinghurst.

Farmer, Donald Fordyce, M.B., B.S., 1944 (Univ. Sydney), Royal North Shore Hospital, St. Leonards.

Finley, Adrian Geoffrey, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.

Fisher, Elizabeth Mary Maxwell, M.B., B.S., 1944 (Univ. Sydney), Bathurst District Hospital, Bathurst.

Fitzhardinge, Grantley William, M.B., B.S., 1944 (Univ. Sydney), Prince Henry Hospital, Little Bay.
Frecker, Brian Eric, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Freeman, Zelman Samuel, M.B., B.S., 1944 (Univ. Sydney), Sydney Hospital, Sydney.
Furber, John Frederick Maynard, M.B., B.S., 1944 (Univ. Sydney), Prince Henry Hospital, Little Bay.
Furber, Thomas Rupert Maynard, M.B., B.S., 1944 (Univ. Sydney), Prince Henry Hospital, Little Bay.
Gayst, Henry, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Gibson, Richard Maxwell, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Gollan, Keith Ransome, M.B., B.S., 1944 (Univ. Sydney), Royal North Shore Hospital, St. Leonards.
Gordon, Alwyce Betty, M.B., B.S., 1944 (Univ. Sydney), Royal North Shore Hospital, St. Leonards.
Graham, Donald James, M.B., B.S., 1944 (Univ. Sydney), Lewisham Hospital, Lewisham.
Graham, John Wedgwood, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Gratton-Smith, Padriac, M.B., B.S., 1944 (Univ. Sydney), Lismore Base Hospital, Lismore.
Gray, Ronald Wallace Menzies, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Greenberg, Harris Phillip, M.B., B.S., 1944 (Univ. Sydney), St. George District Hospital, Kogarah.
Gunning, John Phillip, M.B., B.S., 1944 (Univ. Sydney), Newcastle Hospital, Newcastle.
Halliday, Edward James, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Haneman, Benedetto, M.B., B.S., 1944 (Univ. Sydney), Perth General Hospital, Perth, Western Australia.
Hart, Henry Ellard, M.B., B.S., 1944 (Univ. Sydney), Lewisham Hospital, Lewisham.
Henry, Margaret Tress, M.B., B.S., 1944 (Univ. Sydney), St. George District Hospital, Kogarah.
Herlihy, John Joseph, M.B., B.S., 1944 (Univ. Sydney), Western Suburbs Hospital, Croydon.
Hill, Marie Eleanor, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Hornbrook, John Wallis, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Hudson, Roger Selwyn Barrow, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Jones, Lloyd James, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Jordan, Audrey Ella, M.B., B.S., 1944 (Univ. Sydney), Perth General Hospital, Perth, Western Australia.
Kent, Pauline Ashenden, M.B., B.S., 1944 (Univ. Sydney), Wagga Wagga Base Hospital, Wagga Wagga.
Laycock, John Field, M.B., B.S., 1944 (Univ. Sydney), Sydney Hospital, Sydney.
Lee, Eric Bruce, M.B., B.S., 1944 (Univ. Sydney), Saint Vincent's Hospital, Darlinghurst.
L'Estrange, James Michael, M.B., B.S., 1944 (Univ. Sydney), Saint Vincent's Hospital, Darlinghurst.
Leventhal, Frank, M.B., B.S., 1944 (Univ. Sydney), Sydney Hospital, Sydney.
Lewis, Louis Leonard, M.B., B.S., 1944 (Univ. Sydney), St. George District Hospital, Kogarah.
Lindsay, Robert Alfred, M.B., B.S., 1944 (Univ. Sydney), Newcastle Hospital, Newcastle.
Lister, Harvey Alexander John, M.B., B.S., 1944 (Univ. Sydney), Mater Misericordiæ Hospital, North Sydney.
McDonnell, Lawrence Edward, M.B., B.S., 1944 (Univ. Sydney), Sydney Hospital, Sydney.
McKeon, Thelma Joyce, M.B., B.S., 1944 (Univ. Sydney), Canterbury District Hospital.
Mayer, Loris Lucy, M.B., B.S., 1944 (Univ. Sydney), Sydney Hospital, Sydney.
Mendelsohn, Braham Coleman, M.B., B.S., 1944 (Univ. Sydney), Orange Base Hospital, Orange.
Menzies, Bruce Lambton, M.B., B.S., 1944 (Univ. Sydney), Royal North Shore Hospital, St. Leonards.
Mortlock, Jack Mills, M.B., B.S. (Univ. Sydney), Balmain District Hospital, Balmain.
Orr, Gillespie Neil McGilp, M.B., B.S., 1944 (Univ. Sydney), Ryde District Soldiers' Memorial Hospital.
Orr, Patricia Bleakley, M.B., 1944 (Univ. Sydney), Balmain District Hospital, Balmain.
Parker, John Noel, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Pendergast, James Robert, M.B., B.S., 1944 (Univ. Sydney), Saint Vincent's Hospital, Darlinghurst.
Philpott, Iris Gertrude, M.B., B.S., 1944 (Univ. Sydney), Brisbane General Hospital, Brisbane.
Player, Sydney James William, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Potts, Ian Faulkner, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Potts, Theodore Kenneth, M.B., B.S., 1944 (Univ. Sydney), Balmain District Hospital, Balmain.
Quill, Jack Sidney, M.B., B.S., 1944 (Univ. Sydney), Saint Vincent's Hospital, Darlinghurst.
Radeski, Carl, M.B., B.S., 1944 (Univ. Sydney), Royal South Sydney Hospital, Zetland.
Rassmussen, Winifred Ruby, M.B., B.S., 1944 (Univ. Sydney), Launceston General Hospital, Launceston, Tasmania.
Storey, Joan Evelyn, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Stuart, Mary Grace, M.B., B.S., 1944 (Univ. Sydney), Rachel Forster Hospital for Women and Children, Redfern.
Taylor, William George, M.B., 1944 (Univ. Sydney), Royal North Shore Hospital, St. Leonards.
Terrey, George Russell, M.B., B.S., 1944 (Univ. Sydney), Sydney Hospital, Sydney.
Thorburn, Campbell Hastings, M.B., B.S., 1944 (Univ. Sydney), Sydney Hospital, Sydney.
Thwaite, Thomas John, M.B., B.S., 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Tiernan, Justin Michael, M.B., B.S., 1944 (Univ. Sydney), Saint Vincent's Hospital, Darlinghurst.
Turner, Joyce Ingram, M.B., B.S., 1944 (Univ. Sydney), Saint Vincent's Hospital, Darlinghurst.
Twartz, Lucille Patricia Marien, M.B., B.S., 1944 (Univ. Sydney), Rachel Forster Hospital for Women and Children, Redfern.
Van Gelderen, Philip William, M.B., B.S, 1944 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Wells, Rosina, M.B., B.S., 1944 (Univ. Sydney), Manly District Hospital, Manly.
Wilson, Eunice Maisie, M.B., B.S., 1944 (Univ. Sydney), Sydney Hospital, Sydney.
Woolnough, Esther Isla, M.B., B.S., 1944 (Univ. Sydney), 111, Macquarie Street, Parramatta.
Young, Charles Edward, M.B., B.S., 1944 (Univ. Sydney), Fremantle Public Hospital, Fremantle, Western Australia.

Change of Name in Register.

Wiles, Marjorie Booth, M.B., B.S., 1939 (Univ. Sydney), 15, Wharf Road, Gladesville. Name now Granger, Marjorie Booth.
Ridley, Dorothy Edith, M.B., B.S., 1943 (Univ. Sydney), 13, Hector Road, Willoughby. Name now Rutherford, Dorothy Edith.

QUEENSLAND.

THE undermentioned has been registered, pursuant to the provisions of *The Medical Acts*, 1939-1940, of Queensland, as a duly qualified medical practitioner:

Breini, John, M.B., B.S., 1943 (Univ. Sydney), 28, Stokes Street, Townsville.

Obituary.

HELEN JANE SHAW.

WE regret to announce the death of Dr. Helen Jane Shaw, which occurred on October 20, 1944, at Malvern, Victoria.

JAMES ANDREW NEPTUNE SCOTT.

WE regret to announce the death of Dr. James Andrew Neptune Scott, which occurred on October 20, 1944, at Bendigo, Victoria.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

McKenzie, Henry Ian, M.B., B.S., 1940 (Univ. Sydney), NX77287, Captain H. I. McKenzie, H.Q. Squadron, 2/6 Australian Armoured Regiment, Australia.

Eakin, Reay Ignatius, M.B., B.S., 1940 (Univ. Sydney), 55, Dalhousie Street, Haberfield.

Scott-Young, Eileen, M.B., B.S., 1940 (Univ. Sydney), 121, Burns Bay Road, Lane Cove.

Ewart, Charles Colin, M.B., B.S., 1942 (Univ. Sydney), NX201400, Captain C. C. Ewart, 2/15 Field Ambulance, A.I.F., Australia.

Williams, Albert Henry, M.B., 1939 (Univ. Sydney), 71, Chatham Street, Hamilton, via Newcastle.

Frith, Alexander Richard, M.B., B.S., 1942 (Univ. Sydney), NX170759, 2/15 Field Ambulance, A.I.F., Australia.

Radeski, Carl, M.B., B.S., 1944 (Univ. Sydney), Royal South Sydney Hospital, Zetland.

Sharp, Frank Lane Ritchie, M.B., B.S., 1940 (Univ. Sydney), 57, Vaucluse Road, Vaucluse.

Waddell, James Ronald, M.B., B.S., 1943 (Univ. Sydney), NX203566, Captain J. R. Waddell, "ANGAU", Lae.

The undermentioned has applied for election as a member of the Tasmanian Branch of the British Medical Association:

Storey, John Samuel, M.B., B.S., 1943 (Univ. Sydney), Zeehan District Hospital, Zeehan, Tasmania.

Medical Appointments.

Major James Perrins and Dr. Doris Lyne Officer have been appointed members of the Queen's Memorial Infectious Diseases Hospital Board, Victoria.

Books Received.

"Treatment by Manipulation in General and Consulting Practice", by A. G. Timbrell Fisher, M.C., M.B., Ch.B., F.R.C.S. (England); Fourth Edition; 1944. 8½" × 5½", pp. 232, with many illustrations. Price: 16s. net.

"Lectures on Diseases of Children", by Sir Robert Hutchison, Bart., M.D., LL.D., F.R.C.P., and Alan Moncrieff, M.D., F.R.C.P.; Ninth Edition; 1944. London: Edward Arnold and Company. 8½" × 5½", pp. 485, with many illustrations. Price: 21s. net.

"Practical Anæsthetics: For Students, Hospital Residents and Practitioners", by J. Ross Mackenzie, M.D., D.A. (R.C.P. and S. England), with a foreword by W. C. Wilson, M.B., Ch.B., F.R.C.S.E.; 1944. London: Baillière, Tindall and Cox. 8" × 5½", pp. 144, with illustrations. Price: 10s. 6d.

"Sulfonamide Therapy in Medical Practice", by Frederick C. Smith, M.D., M.Sc.(Med.), F.A.P.S., foreword by George Morris Piersol, B.S., M.D.; 1944. Philadelphia: F. A. Davis Company. 9" × 6", pp. 379, with illustrations. Price: 30s.

"The Clinical Application of the Rorschach Test", by Ruth Bochner, M.A., and Florence Halpern, M.A., with an introduction by Karl M. Bowman, M.D.; 1942. New York: Grune and Stratton. 8½" × 5½", pp. 225. Price: 21s.

"Surgery through the Ages: A Pictorial Chronical", by Lejaren 'A Hiller; Text by Paul Benton and John H. Hewlett, with an introduction by Iago Galdston, M.D.; 1944. New York: Books, Incorporated, distributed by Hastings House. 10" × 8", pp. 189, with many illustrations. Price: 27s. 6d.

"The Neurosurgical Patient: His Problems of Diagnosis and Care", by Carl W. Rand; 1944. Springfield: Charles C. Thomas. 9" × 5½", pp. 588, with many illustrations. Price: $4.00, post paid.

"Technic of Electrotherapy and its Physical and Physiological Basis", by Stafford L. Osborne, M.S., Ph.D., and Harold J. Holmquest, B.S., B.S.(M.E.); 1944. Springfield: Charles C. Thomas, Publisher. 8½" × 5½", pp. 799, with many illustrations. Price: $7·50, post paid.

"Recent Advances in Anæsthesia and Analgesia (Including Oxygen Therapy)", by C. Langton Hewer, M.B., B.S. (London), D.A. (England); Fifth Edition; 1944. London: J. and A. Churchill, Limited. 8" × 5", pp. 351, with many illustrations. Price: 18s.

Diary for the Month.

Nov. 7.—New South Wales Branch, B.M.A.: Organization and Science Committee.
Nov. 10.—Queensland Branch, B.M.A.: Council Meeting.
Nov. 13.—Victorian Branch, B.M.A.: Hospital Subcommittee.
Nov. 13.—Victorian Branch, B.M.A.: Finance Subcommittee.
Nov. 14.—Victorian Branch, B.M.A.: Organization Subcommittee.
Nov. 14.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
Nov. 14.—Tasmanian Branch, B.M.A.: Branch Meeting.
Nov. 15.—Western Australian Branch, B.M.A.: Branch Meeting.
Nov. 16.—Victorian Branch, B.M.A.: Executive Meeting.
Nov. 16.—Victorian Branch, B.M.A.: Ethics Subcommittee.
Nov. 16.—South Australian Branch, B.M.A.: Council Meeting.
Nov. 21.—New South Wales Branch, B.M.A.: Medical Politics Committee.
Nov. 22.—Victorian Branch, B.M.A.: Council Meeting.
Nov. 23.—New South Wales Branch, B.M.A.: Clinical Meeting.
Nov. 24.—Queensland Branch, B.M.A.: Council Meeting.
Nov. 28.—New South Wales Branch, B.M.A.: Ethics Committee.
Nov. 30.—New South Wales Branch, B.M.A.: Branch Meeting.
Nov. 30.—South Australian Branch, B.M.A.: Scientific Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such a notification is received within one month.

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